

FORM PTO-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

217925US0XPCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

10/030269

INTERNATIONAL APPLICATION NO.
PCT/JP00/04515

INTERNATIONAL FILING DATE
6 July 2000

PRIORITY DATE CLAIMED
8 July 1999 (earliest)

TITLE OF INVENTION

AMYLOID-BETA PROTEIN AGGREGATION- REGULATING FACTORS

APPLICANT(S) FOR DO/EO/US

OTA Toshio et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Priority Under 35 U.S.C 119
Request for Priority Under 35 U.S.C 119(e)
Sequence Listing (34 pages)
Form PTO-1449

Page 2 of 2

10/030269 Rec'd PCT/PTO JUN 27 2002
PCT #4.

Docket No. 217925US0XPCT

IN RE APPLICATION OF: Toshio OTA et al

SERIAL NO: 10/030,269

FILED: January 8, 2002

FOR: AMYLOID-BETA PROTEIN AGGREGATION REGULATING FACTORS



ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Transmitted herewith is an amendment in the above-identified application.

- ☐ No additional fee is required
- ☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 is claimed.
- ☒ Additional documents filed herewith: Notice to File Missing Parts - Return Copy; Request for Extension of Time (One-Month); Filing of Declaration under 37 CFR 1.53(f); Declaration and Power of Attorney, 20 pages (Executed); Declaration of Yuri HIO, 1 page (Executed); Sequence Listing (Paper); Computer-Readable Sequence Listing (Diskette); Preliminary Amendment and Statement w/Marked-up copy

The Fee has been calculated as shown below:

the Fee has been calculated as shown below.

CLAIMS	CLAIMS REMAINING		HIGHEST NUMBER PREVIOUSLY PAID	NO. EXTRA CLAIMS	RATE	CALCULATIONS	
TOTAL	51	MINUS	20	31	× \$18 =	\$558.00	
INDEPENDENT	2	MINUS	3	0	× \$84 =	\$0.00	
		<input checked="" type="checkbox"/> MULTIPLE DEPENDENT CLAIMS			+ \$280 =	\$280.00	
		TOTAL OF ABOVE CALCULATIONS					\$838.00
		<input type="checkbox"/> Reduction by 50% for filing by Small Entity					\$0.00
		<input type="checkbox"/> Recordation of Assignment				+ \$40 =	\$0.00
		TOTAL					\$838.00

- ☒ A check in the amount of **\$948.00** is attached.
- ☒ Please charge any additional Fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.
- ☒ If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552



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Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 10/00)

07/03/2002 HKAYPAGH 00000073 10030269

01 FC 966 558.00 02
02 FC 966 280.00 0P

Adjustment date: 07/18/2002 RWHITE1
07/03/2002 HKAYPAGH 00000073 10030269
02 FC:968 -280.00 0P

Repln. Ref: 07/18/2002 RWHITE1 0017375100
DAH:150030 Name/Number:10030269
FC: 704 \$280.00 CR

PTO/PC 402 09 SEP 2002

Docket No.: 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
Toshio OTA, et al. : ATTN: BOX SEQUENCE
SERIAL NO: 10/030,269 :
FILED: JANUARY 8, 2002 :
FOR: AMYLOID-BETA PROTEIN AGGREGATION-REGULATING FACTORS

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Correspondence mailed August 8, 2002, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown in the marked-up copy to read as follows:

--18. (Amended) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
- (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.--

--24. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

28. (Amended) A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid- β protein, and,

(b) selecting the candidate compound that regulates the aggregation or deposition of amyloid- β protein.--

--37. (Amended) An isolated polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.--

--42. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

43. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.--

--45. (Amended) An immunological assay comprising the step of: monitoring an immunological reaction between the peptide according to claim 38 and the antibody against the peptide encoded by the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (Amended) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid- β protein, and,

(b) selecting the candidate compound that regulates the aggregation or deposition of amyloid- β protein.--

REMARKS

Claims 18-68 are active in the present application. The amendments contained herein serve only to correct minor typographical errors. No new matter is believed to have been added by this amendment.

Applicants have now submitted a substitute computer-readable Sequence Listing. The sequence information recorded in the substitute computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing filed on June 27, 2002, a copy of which is enclosed herewith for the Office's convenience, along with the date-stamped filing receipt evidencing timely filing thereof. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552



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(703) 413-3000
Fax #: (703) 413-2220
NFO:VKS
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Docket No.: 217925US-0XPCT
Serial No.: 10/030,269

MARKED-UP COPY

IN THE CLAIMS

Please amend the claims as follows:

--18. (Amended) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.--

--24. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring a polynucleotide

encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
- (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,
- (c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],
- (d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,
- (e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and recovering the expression product.

25. (Amended) A method for producing the protein according to claim 19, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
- (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9, and recovering the expression product.--

--27. (Amended) An immunological assay comprising the step of monitoring an immunological reaction between the protein according to claim 19 and the antibody against the protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

43. (Amended) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.--

--45. (Amended) An immunological assay comprising the step of: monitoring an immunological reaction between the peptide according to claim 38 and the antibody against the peptide encoded by the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or

deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
- (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,
- (c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less[.],
- (d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,
- (e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (Amended) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

- (a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid- β protein, and,
- (b) selecting [a] the candidate compound that regulates the aggregation or deposition of amyloid- β protein.--

Docket No.: 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
Toshio OTA, et al. : ATTN: BOX SEQUENCE
SERIAL NO: 10/030,269 :
FILED: JANUARY 8, 2002 :
FOR: AMYLOID-BETA PROTEIN AGGREGATION-REGULATING FACTORS

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Correspondence mailed March 27, 2002, please amend the above-identified application as follows.

IN THE TITLE

Please delete the title on page 1, line 3 and replace with the following title.

AMYLOID- β PROTEIN AGGLUTINATION-CONTROLLING FACTOR

IN THE SPECIFICATION

Please replace the paragraph on page 25, lines 27-33 with the following paragraph.

NT-2 neuron progenitor cells (Stratagene) a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

(2) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)

Please replace the paragraph on page 29, lines 27-28 with the following paragraph.

Example 2: Expression of the proteins promoting or preventing amyloid β protein aggregation

Please replace line 1 on page 30 with the following line.

Example 3: Amyloid β aggregation reaction

Please replace the paragraph on page 30, lines 2-12 with the following paragraph.

The supernatants obtained in Example 2 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of A β 40 and A β 42, which are commonly found in vivo, A β 1-28 consisting of 28 amino acid residues from the N-terminus of A β , which is considered to aggregate to a similar extent as A β 40 and A β 42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.

Please replace the paragraph on page 31, lines 10-11 with the following paragraph.

Example 4: Gene Expression analysis in patients with Alzheimer's disease

Please delete the original Sequence Listing.

Page 37 (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.

IN THE CLAIMS

Please cancel Claims 1-17.

Please add the following new claims.

18. (New) An isolated polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

19. (New) A protein encoded by a polynucleotide according to claim 18.

20. (New) A protein that suppresses or promotes the aggregation of amyloid- β protein, wherein said protein is encoded by a polynucleotide that, from a molecular

polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
- (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,
- (c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.
- (d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,
- (e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, and recovering the expression product.

26. (New) An antibody against the protein according to claim 19.

27. (New) An immunological assay comprising the step of monitoring an immunological reaction between the protein according to claim 19 and the antibody against the protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9.

28. (New) A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid- β protein, and,

(b) selecting a the candidate compound that regulates the aggregation or deposition of amyloid- β protein.

29. (New) A method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to claim 18, wherein said method comprises the following steps of:

(a) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

(i) an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

(b) measuring the presence of the reporter gene, and,

measured in step (b) when compared to the control.

31. (New) A pharmaceutical agent comprising the protein according to claim 19.

33. (New) A pharmaceutical agent comprising an antisense polynucleotide

34. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 28.

(a) measuring the expression of a polynucleotide according to claim 18,

polynucleotide is expressed in healthy subjects and detecting a change in expression,

36. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 28.

37. (New) An isolated polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

38. (New) A peptide encoded by the polynucleotide according to claim 37.

39. (New) A vector comprising the polynucleotide according to claim 37.

40. (New) A transfectant harboring the polynucleotide according to claim 37.

41. (New) A transfectant harboring the vector according to claim 39.

42. (New) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein, and recovering the expression product.

43. (New) A method for producing the peptide claim 38, wherein said method comprises the steps of culturing the transfectant harboring the vector comprising the polynucleotide encoding a partial peptide of a protein encoded by a polynucleotide encoding

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein functionally equivalent to the protein of (b) comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added, wherein the overall percentage of mutations is typically 10% or less.

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO, 1, 3, 5, 7 or 9, wherein said partial peptide (a) suppresses or promotes amyloid- β protein aggregation, or (b) is used to provide a specific antibody against the whole protein.

46. (New) A method of screening for a compound that regulates the activity of a peptide encoded by the polynucleotide according to claim 37, wherein, said method comprises the following steps of:

(a) contacting a candidate compound with said protein, or with a cell expressing said protein, in the presence of amyloid- β protein, and,

(b) selecting a the candidate compound that regulates the aggregation or deposition of amyloid- β protein.

47. (New) A method of screening for a compound that regulates expression of a peptide encoded by a polynucleotide according to claim 37, wherein said method comprises the following steps of:

(a) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:

(i) an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,

(ii) a reporter gene operably linked downstream of the expression regulatory region,

(b) measuring the presence of the reporter gene, and,

(c) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control.

48. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 46.

49. (New) A pharmaceutical agent comprising the peptide according to claim 38.

50. (New) A pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of the polynucleotide according to claim 37.

51. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 46.

52. (New) A method for detecting Alzheimer's disease, comprising the following steps of:

- (a) measuring the expression of a polynucleotide according to claim 37,
- (b) comparing the measurement obtained in (a) with that obtained when the polynucleotide is expressed in healthy subjects and detecting a change in expression,
- (c) linking Alzheimer's disease with said change in expression of the polynucleotide.

[illegible]

54. (New) A polynucleotide comprising a polynucleotide according, or a nucleotide sequence complementary to the complementary strand of the polynucleotide, according to claim 18, wherein said polynucleotide comprises at least 15 nucleotides.

55. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 29.

56. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 29.

57. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a protein according to claim 19.

58. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a protein according to claim 20.

59. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 29.

60. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the protein according to claim 19.

61. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the protein according to claim 20.

62. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 18.

63. (New) A pharmaceutical agent comprising a compound obtained by the method according to claim 47.

64. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a compound obtained by the method according to claim 47.

65. (New) A pharmaceutical agent for prevention or treating of Alzheimer's disease, wherein said pharmaceutical agent comprising a peptide according to claim 38.

66. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient a compound obtained by the method according to claim 47.

67. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient the peptide according to claim 38.

68. (New) A method for preventing or treating Alzheimer's disease, wherein the method comprises administering a pharmaceutical composition comprising as an active ingredient an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 37.

REMARKS

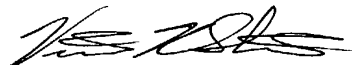
Claims 18-68 are active in the present application. Claims 1-17 have been cancelled. Claims 18-68 are new claims. Support for the new claims is found in the original claims and throughout the specification. New Claims 37-54 are drawn to a partial peptide. Support for claims to a partial peptide can be found in the specification on page 8, lines 21-23. No new matter is believed to have been added by this amendment.

Applicants have now submitted a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. The sequence information recorded in the corresponding computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing. Support for all of the sequences listed in the substitute Sequence Listing is found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552

(703) 413-3000
Fax #: (703) 413-2220
NFO:SUK:VKS
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Docket No.: 217925US-0XPCT
Serial No.: 10/030,269

MARKED-UP COPY

IN THE TITLE

Please delete the title on page 1, line 3 and replace with the following title.

[AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS]

--AMYLOID- β PROTEIN AGGLUTINATION-CONTROLLING FACTOR--

IN THE SPECIFICATION

Please replace the paragraph on page 25, lines 27-33 with the following paragraph.

--NT-2 neuron progenitor cells (Stratagene) a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

[(3)] (2) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)--

Please replace the paragraph on page 29, lines 27-28 with the following paragraph.

--Example [5] 2: Expression of the proteins promoting or preventing amyloid β protein aggregation--

Please replace line 1 on page 30 with the following line.

--Example [6] 3: Amyloid β aggregation reaction--

Please replace the paragraph on page 30, lines 2-12 with the following paragraph.

--The supernatants obtained in Example [5] 2 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were

conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of A β 40 and A β 42, which are commonly found in vivo, A β 1-28 consisting of 28 amino acid residues from the N-terminus of A β , which is considered to aggregate to a similar extent as A β 40 and A β 42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.--

Please replace the paragraph on page 31, lines 10-11 with the following paragraph.

--Example [6] 4: Gene Expression analysis in patients with Alzheimer's disease--

Please delete the original Sequence Listing.

Page 37 (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.

IN THE CLAIMS

Claims 1-17 (Cancelled).

Claims 18-68 (New).



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DESCRIPTION

AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS

5 Technical Field

The present invention relates to proteins that suppress or promote the aggregation or deposition of amyloid- β protein (also referred to as " $A\beta$ " hereinafter), polynucleotides encoding the proteins, a method for preparing the proteins using the polynucleotides, an
10 expression system for producing the proteins, and a method of screening for a compound that suppresses or promotes the aggregation of amyloid- β protein using the expression system. The present invention also relates to a method for preventing and treating Alzheimer's disease using proteins obtained by the method above, or a compound obtained
15 by the screening method.

Background Art

Alzheimer's disease is a disorder associated with cognitive dysfunctions, and is characterized by a loss of nerve cells and emergence
20 of a large number of senile plaques and neurofibrillary tangles. Senile plaques are detected at the earliest stage of development of this disease. These plaques are highly specific to this disease since they are not found in other neurodegenerative disorders. Amyloid- β protein ($A\beta$) is the major constituent of senile plaques and forms amyloid fibrils
25 having a β -sheet structure. $A\beta$ is a polypeptide comprising approximately 40 amino acid residues and has a molecular weight of 4,000 Da. It easily aggregates to form fibrils and becomes insoluble. The major molecular species of this protein are $A\beta$ 40, which ends with valine at amino acid residue 40, and $A\beta$ 42, the longer form of $A\beta$ having
30 two additional residues. Although $A\beta$ is usually degraded and never accumulates in the brain, the degrading capacity decreases with aging, causing an accumulation of $A\beta$. This triggers neuronal dysfunction and cell death, ultimately resulting in dementia and Alzheimer's disease. Through various genetic analyses and molecular biological
35 and neuropharmacological studies, "amyloid hypothesis" has been proposed as a cause of the pathogenesis of Alzheimer's disease.

Disclosure of the Invention

An objective of the present invention is to provide proteins that suppress or promote aggregation or deposition of amyloid- β protein, and polynucleotides encoding these proteins. A further objective of the present invention is to provide a method for treating Alzheimer's disease by discovering a method or substance that suppresses or promotes aggregation or deposition of amyloid- β protein.

To achieve the above objectives, the present inventors conducted extensive studies and finally discovered polynucleotides encoding secretory or membrane-bound forms of proteins that suppress or promote the aggregation or deposition of amyloid- β protein, and hence completed the present invention.

Thus, the present invention relates to:

[1] a polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,

(b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,

(c) a polynucleotide that encodes a protein comprising an amino acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added,

(d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9; or,

(e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9;

[2] a polynucleotide encoding a partial peptide of the protein encoded by a polynucleotide according to [1];

[3] a peptide or protein encoded by a polynucleotide according to [1] or [2];

[4] a protein that suppresses or promotes the aggregation of amyloid- β

protein, wherein said protein is encoded by a polynucleotide that, from a molecular evolutionary aspect, originated from the same gene from which a polynucleotide according to [1] originated from;

[5] a vector comprising a polynucleotide according to [1] or [2];

5 [6] a transfectant harboring a polynucleotide according to [1] or [2] or the vector according to [5];

[7] a method for producing the peptide or protein according to [3], wherein said method comprises the steps of: culturing the transfectant according to [6], and recovering the expression product;

10 [8] a polynucleotide comprising a polynucleotide according to [1] or [2] or a nucleotide sequence complementary to the complementary strand of the polynucleotide according to [1] or [2], wherein said polynucleotide comprises at least 15 nucleotides;

[9] an antibody against the peptide or protein according to [3];

15 [10] an immunological assay comprising the step of: monitoring an immunological reaction between the peptide or protein according to [3] and the antibody according to [9];

[11] a method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to [1], wherein
20 said method comprises the following steps of:

contacting a candidate compound with a protein encoded by a polynucleotide according to [1], or with a cell expressing said protein, in the presence of amyloid- β protein, and,

25 selecting the candidate compound that regulates the aggregation or deposition of amyloid- β protein;

[12] a method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to [1], wherein said method comprises the following steps of:

(1) contacting a candidate compound with a cell, wherein a vector
30 has been introduced into said cell, said vector comprising:
an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and,
35 a reporter gene operably linked downstream of the expression regulatory region,

(2) measuring the activity of the reporter gene, and,

(3) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control;

[13] a pharmaceutical agent comprising a compound obtained by the method according to [11] or [12];

[14] a pharmaceutical agent comprising the peptide or protein according to [3] or [4];

[15] a pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to [1];

[16] the pharmaceutical agent according to [13] or [14], wherein said pharmaceutical agent is a preventive or therapeutic agent for Alzheimer's disease; and,

[17] a method for detecting Alzheimer's disease, comprising the following steps of:

(1) measuring the expression of a polynucleotide according to [1];

(2) comparing the measurement obtained by (1) with that obtained when the polynucleotide is expressed in healthy subjects; and,

(3) linking Alzheimer's disease with said change in expression of the polynucleotide.

The proteins of the present invention that suppress or promote the aggregation of amyloid- β protein, and the polynucleotides encoding the proteins comprise the whole or part of the sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9.

The polynucleotides of the present invention may include any nucleotide that can encode the proteins of the present invention, such as genomic DNA and chemically-synthesized DNA as well as cDNA, but are not limited thereto. The polynucleotides of the present invention may also include polynucleotides having any nucleotide sequence that is based on the degeneracy of the genetic code, as long as the polynucleotides encode the proteins of the present invention. The polynucleotides encoding the proteins of the present invention may be isolated by conventional methods, such as hybridization using as a probe a polynucleotide sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9, or a partial sequence thereof, or PCR using primers designed

based on the information of these sequences.

A protein of the present invention that suppresses or promotes amyloid- β protein aggregation, can be obtained by expressing the protein in a transformant using an expression vector comprising the open reading frame within the sequence shown in, for example, SEQ ID NO. 1, 3, 5, 7 or 9. These expressed proteins may be purified and isolated, using conventional methods, from the culture or cell fraction. Specifically, methods for purification and isolation are, for example, as follows: first, the cells or supernatant is collected using conventional methods, such as filtration and centrifugation, and the cell membranes and/or the cell walls are then treated by sonication and/or with lysozyme to obtain a cell membrane fraction. Subsequently, the cell membrane fraction thus obtained is dissolved in a suitable solution. From the supernatant or the cell membrane fraction, the protein of the invention is isolated and purified according to conventional methods generally used for purification and isolation of a natural or synthetic protein. Examples of methods for isolation or purification include dialysis, gel filtration, affinity chromatography using a monoclonal antibody against the proteins of the present invention or a partial peptide thereof, column chromatography using an appropriate absorbent, high performance liquid chromatography, etc.

Furthermore, the present invention includes polynucleotides encoding proteins functionally equivalent to the proteins described above. As used herein, the term "functionally equivalent" means that the protein of interest has an activity that suppresses or promotes amyloid- β protein aggregation. The activity that suppresses or promotes amyloid- β protein aggregation can be confirmed by using, for example, the methods described in the working examples. A β and its fragments are prone to aggregate under particular conditions. Addition of a test compound under such conditions would give rise to A β aggregates, if the test compound had a property that promotes aggregation. A fragment comprising the N-terminal amino acid sequence (residues 1-28) of A β has been used in experiments of this sort as a partial peptide having A β -aggregating activity (Methods in Enzymology Vol. 309, 274-284, 1999). A β aggregation can be detected optically,

or can be confirmed microscopically after staining with Congo red and such.

One skilled in the art would be able to prepare proteins functionally equivalent to the proteins used in the β -amyloid aggregation tests described in the working examples below, for example, by using a method for introducing mutations into the amino acid sequences of proteins (e.g. site-directed mutagenesis, Current Protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wily & Sons Section 8.1-8.5). Such proteins might occur due to spontaneous mutation of amino acids in nature. The present invention also includes a protein having an amino acid sequence in which one or several amino acid residues are different from those found in a sequence of any one of the proteins identified in the working examples below (SEQ ID NO. 2, 4, 6, 8 or 10, or the amino acid sequence encoded by SEQ ID NO. 1, 3, 5, 7 or 9) due to a substitution, deletion, insertion and/or addition, as long as the protein retains a function equivalent to the proteins identified in the working examples below.

Number or sites of amino acid mutations in the protein are not limited, as long as the protein function is retained. The number (percentage) of mutations is typically 10% or less, preferably 5% or less, and more preferably 1% or less of the total amino acids. Alternatively, the mutation of "several" amino acids as used in the present invention includes the mutation of a "few" amino acids as well. "Few" refers to, for example, five, four, three, two, or one amino acid. Preferably, in view of maintaining protein function, substituting amino acids may have properties similar to the amino acids to be substituted. For example, Ala, Val, Leu, Ile, Pro, Met, Phe, and Trp are all classified into nonpolar amino acids, and they are thought to share common properties. Uncharged amino acids include Gly, Ser, Thr, Cys, Tyr, Asn, and Gln. Acidic amino acids include Asp and Glu, and basic amino acids include Lys, Arg, and His.

Alternatively, a protein functionally equivalent to the protein identified in the working examples below can be isolated using a hybridization or gene amplification technique well known to one skilled in the art. More specifically, using the hybridization technique (Current Protocols in Molecular Biology edit. Ausubel et al. (1987)

Publish. John Wiley & Sons Section 6.3-6.4), one skilled in the art would routinely be able to isolate a polynucleotide showing a significant homology to any one of the polynucleotide sequences encoding the proteins identified in the working examples below (SEQ ID NO. 1, 3, 5, 7 or 9) by using a polynucleotide sequences, or a portion thereof, and obtain a functionally equivalent protein from the polynucleotide isolated. The present invention includes a protein encoded by a polynucleotide hybridizing to a polynucleotide encoding a protein identified in the working examples below, as long as the proteins are functionally equivalent. A functionally equivalent protein can be isolated from animals including, but not limited to, vertebrates such as humans, mice, rats, rabbits, pigs, and cattle. From these animals, one can isolate genes that originated from molecular-evolutionarily the same gene that encodes a protein of the present invention that suppresses or promotes amyloid β protein aggregation. As used herein, the term "genes that originated from molecular-evolutionarily the same gene" refers to genes that are rationally judged to have evolved from one ancestor gene from which the human gene of the present invention evolved in the course of molecular-evolution. This judgment is based on polynucleotide sequence analysis of the genes or analysis of their physiological roles and such. Such genes maintain a significant nucleotide sequence homology among them.

Stringent hybridization conditions for isolating a polynucleotide encoding a functionally equivalent protein are, typical washing conditions such as "1X SSC, 0.1% SDS, 37°C". More stringent conditions are, for example, "0.5X SSC, 0.1% SDS, 42°C", and even more stringent conditions are, for example, "0.1X SSC, 0.1% SDS, 65°C". The more stringent the hybridization conditions become, the more homologous to the probe sequence the polynucleotide is expected to be. Note that the above combinations of SSC, SDS, and temperature are given only for illustration, and one skilled in the art can achieve the same level of stringency by combining these factors appropriately to determine the hybridization conditions. The factors include those described above, or other factors (e.g. probe concentrations, length of probes, reaction time, etc.).

In general, a protein isolated using such hybridization techniques shows a significant homology in the nucleotide sequence encoding the protein, or in its amino acid sequence, compared to the sequence of a protein of the present invention, shown in SEQ ID NO. 2, 4, 6, 8 or 10, or a protein encoded by the a sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9. "Significant homology" refers to a sequence identity of at least 60% or more, preferably 70% or more, more preferably 80% or more, even more preferably 90% or more, and most preferably 95% or more. Sequence homology can be determined using the BLAST 2 search algorithm (Altschul, S.F. et al, 1997, Gapped BLAST and PSI-BLAST: a new generation of protein database search programs, Nucleic Acids Res. 25: 3389-3402).

A gene-amplification technique (PCR) (Current protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wiley & Sons Section 6.1-6.4) can be used to design primers based on a part of any of the polynucleotide sequences identified in the working examples below (SEQ ID NO. 1, 3, 5, 7 or 9), and to isolate a polynucleotide fragment that shows a significant homology to the above polynucleotide sequence or a portion thereof, to obtain a protein functionally equivalent to the protein identified in the working examples.

The present invention also relates to a partial peptide of the proteins of the present invention and to a polynucleotide encoding the partial peptide. A partial peptide of the present invention comprises at least 7 amino acid residues, preferably 9 or more amino acid residues, more preferably 12 or more amino acid residues, even more preferably 15 or more amino acid residues. The partial peptide of the present invention may be produced by, for example, genetic engineering, a well-known technique for peptide synthesis, or cleavage of the proteins of the present invention with an appropriate peptidase.

The present invention also provides expression vectors comprising any one of the polynucleotides mentioned above. Furthermore, the present invention relates to transfectants harboring any of the expression vectors or polypeptides mentioned above, and a method for producing proteins or partial peptides thereof that suppress or promote amyloid- β protein aggregation. Such a method comprises culturing the transfectant and isolating a protein of the

present invention from the culture. Moreover, the present invention provides the protein or partial peptide produced by the above method.

When producing polypeptides by means of genetic recombination, the type and extent of glycosylation of a polypeptide of interest would differ depending on the type of host cell. Furthermore, in the method of so-called "secretory production" of polypeptides, it is well known to one skilled in the art that (N- and/or C-) terminal amino acid sequences of precursor peptides expressed in host cells would undergo processing by signal peptidases and such to produce polypeptides having various terminal sequences. Therefore, one skilled in the art would easily understand that such polypeptides are also included in the proteins of the present invention.

The working examples described below illustrates only an example of constructing a vector that functions in mammalian cells as an expression vector. However, since the polynucleotide sequences encoding the proteins of the present invention are disclosed herein, it would be easy for one skilled in the art to construct an expression vector that can express and produce a protein of the present invention when such a vector is introduced into a fungal host cell, such as a yeast, or a prokaryotic host cell. Therefore, the present invention includes expression vectors constructed using any methods known in the art based on the polynucleotide sequences of the present invention.

Microbial cells that can be used for the expression of the polynucleotides encoding the proteins of the present inventions include, for example, prokaryotic bacteria (e.g. *Escherichia coli* and *Bacillus subtilis*) and eukaryotic yeasts (e.g. *Saccharomyces cerevisiae*). Mammalian cells include cultured human cells and cultured animal cells. Moreover, cultured plant cells can be used.

Examples of microorganisms include bacteria of the genus *Escherichia* (e.g. *E. coli* HB101 ATCC 33694, *E. coli* HB101-16 FERM BP-1872, *E. coli* MM294 ATCC 31446, *E. coli* DH1 ATCC 33849, etc.) and baker's yeast (e.g. *S. cerevisiae* AH22 ATCC 38626, etc.). Examples of mammalian cells include HEK293 cells derived from human embryonic kidney cells, mouse L929 cells, Chinese hamster ovary (CHO) cells, etc.

Generally, expression vectors are constructed with, at least,

a promoter, an initiation codon, a polynucleotide encoding the amino acid sequence of any of the proteins of the present invention, a termination codon, and a self-replication unit, when prokaryotes, bacteria, particularly *E. coli* are used as host cells. When eukaryotic
5 cells such as yeast and mammalian cells are used, expression vectors are preferably constructed with, at least, a promoter, an initiation codon, a polynucleotide encoding the amino acid sequence of any of the proteins of the present invention, and a termination codon. Additionally, an enhancer sequence, 5'- and 3'-untranslated regions
10 for the proteins of the present invention, a polyadenylation site, and a self-replication unit may be integrated.

The self-replication unit preferably comprises a selectable marker for transfectants (e.g. resistance to ampicillin). In the case of expression vectors using bacteria as host cells, the term "promoter"
15 means a promoter-operator region containing a promoter, operator, and a Shine-Dalgarno (SD) sequence (e.g. AAGG, etc.). Examples of such promoters include conventional promoter-operator regions (e.g. the lactose operon, PL-promoter, trp-promoter, etc.). An Example of a promoter for expression vectors used in yeast host cells includes
20 the *pho5* promoter. Additionally, to facilitate purification, basic amino acids having affinity for chelated metal ions can be added to either end of a protein of the present invention.

When basic amino acids are added, a primer having, at its 5'-end, a nucleotide sequence sequentially coding for desired amino acid
25 residues can be used for PCR to introduce an oligonucleotide at either end of a gene of interest. Histidine, lysine, arginine, and such can be used as basic amino acids.

Examples of promoters used in expression vectors in mammalian cells include the HTLV-LTR promoter, early and late SV40 promoters, CMV promoters, the mouse metallothionein I (MMT) promoter, etc. A
30 preferred example of an initiation codon is the methionine codon (ATG).

A polynucleotide encoding an amino acid sequence of the proteins of the present invention may be obtained by, for example, partial or complete synthesis of nucleotides using a DNA synthesizer.
35 Alternatively, it can be obtained from a human cDNA library by using a probe or primer set that is designed based on a nucleotide sequence

as shown in SEQ ID NO. 1, 3, 5, 7 or 9. The genomic DNA encoding the proteins of the present invention can also be prepared by treating genomic DNA according to a conventional method (e.g. digestion with restriction enzymes, dephosphorylation by bacterial alkaline phosphatase, phosphorylation by T4 polynucleotide kinase, and ligation with T4 DNA ligase). Furthermore, the genomic DNA thus obtained can be used to demonstrate the transcriptional initiation site of a gene of the present invention located on the genome. This allows one to specify expression-regulatory regions located upstream of the gene. Regulatory regions, such as promoters and enhancers, which would control expression of the a encoding a protein of the present invention, are useful as target regions for detecting aberrant expression of a protein of the present invention. Regulation of gene expression can be achieved using decoy nucleotide pharmaceuticals that target such regions.

The host cells of the present invention include cells used for functional analysis of the proteins of the present invention and those used for screening inhibitors or enhancers of the functions of the proteins. Introduction of a vector into host cells may be conducted using any of the methods including, for example, calcium phosphate precipitation, electroporation (Current protocols in Molecular Biology edit. Ausubel et al. (1987) Publish. John Wiley & Sons. Section 9.1-9.9), the lipofectamine method, and microinjection. Preparation of the proteins of the present invention from transfectants may be conducted using any of the isolation and purification methods well known to one skilled in the art.

The present invention also provides a polynucleotide comprising at least 15 nucleotides, which is complementary to any of the polynucleotide sequences shown in SEQ ID NO. 1, 3, 5, 7, or 9, or to a complementary strand thereof. As used herein, the term "complementary strand" refers to one strand of a double-stranded polynucleotide that forms base pairs of A:T (A:U) and G:C with the other strand of the polynucleotide. Also, "complementary" is defined as not only sequences that completely match a continuous nucleotide region of at least 15 nucleotides, but also sequences having a homology of at least 70%, preferably 80% or more, more preferably 90% or more,

and most preferably 95% or more to that region. Sequence homology can be determined according to the algorithm as described in this description.

Such a polynucleotide can be used as a probe for isolating and
 5 detecting the DNA or RNA encoding a protein of the invention, or as
 a primer for amplifying a polynucleotide. When used as a primer, the
 DNA usually comprises 15-100 bp, and preferably, 15-35 bp. When used
 as a probe, the DNA comprises the entire sequence of a DNA of the
 invention, or at least a part of it, and comprises at least 15 bp.
 10 When used as a primer, the 3'-region of the polynucleotide must be
 complementary, but the 5'-terminal may contain additional sequences,
 such as a restriction enzyme recognition site or a tag.

The polynucleotides of the present invention can be used for
 testing or diagnosing aberrations in the proteins of the present
 15 invention. For example, the polynucleotides of the present invention
 can be used as probes or primers to test aberrations in gene expression
 by Northern hybridization or RT-PCR. As used herein, the term
 "expression" includes transcription and/or translation. Expression
 analysis of the polynucleotides of the present invention may allow
 20 the testing and diagnosing of gene expression at the transcriptional
 level. Gene expression at the translational level may be tested or
 diagnosed by using antibodies raised against the proteins of the present
 invention as described below. Polymerase chain reaction (PCR) using
 as a primer a polynucleotide of the present invention, such as genomic
 25 DNA-PCR and RT-PCR, can amplify a polynucleotide encoding a protein
 of the present invention or an expression regulatory region. Sequence
 aberrations can be tested or diagnosed using RFLP analysis, SSCP,
 sequencing, and such.

Moreover, "a polynucleotide comprising at least 15 nucleotides,
 30 which is complementary to any of the polynucleotide sequences as set
 forth in SEQ ID NO. 1, 3, 5, 7 and 9, or to a complementary strand
 thereof" include antisense polynucleotides for inhibiting the
 expression of the proteins of the present invention. Antisense
 polynucleotides comprise at least 15 bp or more, preferably 100 bp
 35 or more, more preferably 500 bp or more, and usually 3000 bp or less,
 preferably 2000 bp or less.

Such antisense polynucleotides are expected to be applied in gene therapy for diseases caused by aberrations (in function or expression) in the proteins of the present invention. Specifically, in Alzheimer's disease, the aggregation and deposition of amyloid- β protein trigger the disease and lead to the cell death of cranial nerve cells and neural dysfunctions. Therefore, if the expression of a protein of the present invention that promotes amyloid- β protein aggregation can be inhibited, it may be useful in the treatment or prevention of Alzheimer's disease. In addition, an Alzheimer's disease model system can be produced if the expression of a protein of the present invention that suppresses amyloid- β protein aggregation can be inhibited, which will result in the promotion of amyloid- β protein aggregation. An antisense polynucleotide can be prepared, for example, by utilizing the phosphorothioate method based on the sequence information of a polynucleotide sequence shown in SEQ ID NO. 1, 3, 5, 7 or 9 ("Physicochemical properties of phosphorothioate oligodeoxynucleotides." Stein (1988) Nucleic Acids Res. 16: 3209-3221).

A polynucleotide or antisense polynucleotide of the present invention can be used in gene therapy, for example, by administering it to a patient by utilizing the in vivo or ex vivo method using vectors such as retrovirus vectors, adenovirus vectors, and adeno-associating virus vectors, or non-virus vectors such as liposomes.

The present invention also relates to an antibody capable of binding to a protein of the invention. The form of the antibody is not especially restricted; it includes polyclonal antibodies, monoclonal antibodies, or portions thereof, which are capable of binding to an antigen. It also includes antibodies of all classes. Furthermore, specialized antibodies such as humanized antibodies are also included.

If the antibody is a polyclonal antibody, it can be obtained according to the standard method by synthesizing a protein of this invention, or a partial peptide thereof, and immunizing rabbits with the protein or peptide (Current Protocols in Molecular Biology (1987) Ausubel et al. edit, John Wily & Sons, Section 11.12-11.13). If the

antibody is a monoclonal antibody, it can be obtained by immunizing mice with a protein of this invention, or a partial peptide thereof, and producing a hybridoma cell by fusing spleen cells and myeloma cells (Current Protocols in Molecular Biology (1987) Ausubel et al. edit, John Wiley & Sons, Section 11.4-11.11).

An antibody capable of binding to a protein of the present invention can be used for purifying a protein of the invention, and also for detecting and/or diagnosing aberrations in the expression and the structure of the protein. Specifically, proteins may be extracted from tissues, blood, or cells, and methods such as western blotting, immunoprecipitation, or ELISA can be used for the above purpose.

Furthermore, an antibody capable of binding to the proteins of the present invention may be utilized for treating diseases associated with the protein. If the antibody is used for treating patients, a human antibody or humanized antibody is desirable in terms of their low antigenicity. Human antibodies can be prepared by immunizing a mouse in which the immune system has been replaced with that of a human ("Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice" Mendez M.J. et al. (1997) Nat. Genet. 15: 146-156, for a reference). Humanized antibodies can be prepared by recombination of the hyper variable region of a monoclonal antibody (Methods in Enzymology (1991) 203: 99-121).

Among the proteins of the present invention, the proteins encoded by the polynucleotides of SEQ ID NOs. 1, 3 and 7 have an inhibitory activity on amyloid- β protein aggregation, and as shown in the Examples below, their expression decreases in patients with Alzheimer's disease. Therefore, augmentation of the expression level of these proteins will prevent amyloid- β protein aggregation, and will be useful for the treatment and prevention of Alzheimer's disease. Additionally, these proteins, and their functional equivalents, can themselves be used as therapeutic and preventive agents for Alzheimer's disease.

Among the proteins of the present invention, the proteins encoded by the polynucleotides of SEQ ID NOs. 5 and 9 have an enhancing activity on amyloid- β protein aggregation, as shown in the working examples

below, and their expression increases in patients with Alzheimer's disease. Therefore, reduction of the expression level of these proteins will prevent amyloid- β protein aggregation, and will be useful for the treatment and prevention of Alzheimer's disease.

5 Moreover, the proteins of the present invention are expected to relate to other amyloidoses, specifically, schizophrenia and related neuropathies, rheumatoid arthritis, tuberculosis, leprosy, bronchitis, systemic lupus erythematosus (SLE), dialysis amyloidosis, diabetic amyloidosis, atrial amyloidosis, and such, and they can be
10 used as therapeutic and preventive agents for these diseases, or for screening such therapeutic and preventive agents.

 The present invention provides a method of screening for compounds regulating the activity of the proteins of the present invention. Since the proteins of the present invention prevent or
15 promote amyloid- β protein aggregation, such compounds may be useful as therapeutic and preventive agents for Alzheimer's disease by regulating the expression of the gene products. This screening is conducted as follows.

 A candidate compound that can prevent amyloid- β protein
20 aggregation may be selected by contacting the candidate compound with a protein of the present invention, or cells expressing the protein, under conditions that permit amyloid- β protein aggregation.

 More specifically, any of the proteins of the present invention, for example, a protein encoded by the nucleotide sequence of SEQ ID
25 NO. 1, 3, 5, 7 or 9, or a protein functionally equivalent to the protein, or a cell expressing the protein, is incubated with a candidate compound in a solution containing amyloid- β protein ($A\beta$ 40, $A\beta$ 42, $A\beta$ 28, etc.). Subsequently, to determine the degree of aggregation, fluorescence intensity is measured using a fluorescent dye such as thioflavin-T,
30 which binds to, for example, aggregated amyloid- β protein.

 Among the proteins of the present invention, the increase of the expression of a protein encoded by a polynucleotide as set forth in SEQ ID NOs. 1, 3 or 7 would inhibit amyloid- β protein aggregation and thus be useful for the treatment and prevention of Alzheimer's
35 disease. . A reduction of the expression of a protein encoded by a polynucleotide as set forth in SEQ ID NOs. 5 or 9 would prevent amyloid- β

protein aggregation, and thus is useful for the treatment and prevention of Alzheimer's disease. Therefore, compounds that can regulate the expression of the genes encoding the proteins of the present invention are useful as therapeutic and preventive agents. Thus, the present invention relates to a method of screening for a compound that can regulate the expression of a protein encoded by a polynucleotide of the present invention, which method comprises the following steps of:

- (1) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:
 - an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, and,
 - a reporter gene operably linked downstream of the expression regulatory region,
- (2) measuring the activity of the reporter gene, and,
- (3) selecting the candidate compound that increases or decreases the reporter activity measured in step (2) when compared to the control.

To carry out the screening method of the present invention, a regulatory region of the gene is isolated from chromosomal DNA, and an expression plasmid is prepared in which a reporter gene (e.g. luciferase, β -galactosidase, GFP (green fluorescent protein), etc.) is linked downstream of the regulatory region. A regulatory region that controls expression of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9 may be cloned from chromosomal DNA by any method well known in the art. For example, S1 mapping is well known as a method for specifying transcription initiation sites ("Isolation of Transcriptional Regulatory Region" and "Isolation and Purification of Transcription Factors" in Department Oncology, The Institute of Medical Science (ed.), "Current Protocols for Cellular Engineering", Cell Technology, Separate Volume 8, pp. 362-374, Shujunsha Co. Ltd., 1993). In general, screening of a human genomic library using a 15-100bp, preferably 30-50bp fragment at the 5' terminus of the gene may allow cloning of the DNA for the regulatory region controlling gene expression as a cloned gene comprising the expression regulatory region. The cloned DNA thus obtained often contains 10

kb or longer sequence of the 5'-untranslated region of the gene. Then, the 5'-terminal region of the cloned DNA is shortened or fragmented by treating with, for example, an exonuclease. The minimal unit essential for maintaining the activity of the regulatory region can be found by evaluating the expression level or regulation of expression of the reporter gene using a sequence comprising a shortened expression regulatory region (deletion study). A computer program that predicts expression-regulatory regions of genes using Neural Network is widely known (http://www.fruitfly.org/seq_tools/promoter.html, Reese, M.G., et al, "Large Scale Sequencing Specific Neural Networks for Promoter and Splice Site Recognition" Biocomputing: Proceedings of the 1996 Pacific Symposium, edited by Lawrence Hunter and Terri E. Klein, World Scientific Publishing Co, Singapore, January 2-7, 1996). Alternatively, the minimal unit essential for maintaining the activity is predicted using a program such as the Promoter Scan program that searches for a transcription factor binding sequence and predicts the expression regulatory region (<http://biosci.cbs.umn.edu/software/proscan/promoterscan.htm>, Prestridge, D.S. 1995, Prediction of Pol II Promoter Sequence using Transcription Factor Binding Sites. J. Mol. Biol. 249: 923-932). The deletion study can be conducted, focusing on the core regions predicted.

An expression plasmid in which a reporter gene is operably linked downstream of the thus isolated gene for the regulatory region is constructed and introduced into an appropriate cell. As used herein, the term "operably linked" means that the two elements are linked so that transcription of the reporter gene is initiated by activation of the above expression regulatory region. Any gene may be used as a reporter gene as long as it encodes a protein that allows one to observe an activation of the above regulatory region as an expression of the gene. Particularly, genes such as luciferase, β -galactosidase, GFP (Green Fluorescent Protein) are typically used as reporter genes. Mammalian cells having a deletion in the corresponding gene, for example, can be used as cells for introducing the vector. Next, mammalian cells having a deletion in the corresponding gene, for example, are transfected with the expression plasmid. Expression of the reporter gene resulting from transcriptional activation by the regulatory

region may be detected as a color development, luminescence, and so on. Under these conditions, this cell strain is seeded into a 96-well multiplate and compounds to be screened are added to each well, thereby allowing easy selection of compounds that can prevent or promote the expression of gene products. As a method for selecting a compound, if GFP is used as the reporter gene, the fluorescence intensities between the presence and absence of the compound can be compared. Comparison refers to when the luminescence ration is two-folds or higher, or 1/2 or lower, preferably five-folds or higher, or 1/5 or lower, and more preferably 10-folds or higher, or 1/10 or lower. This method can be applied to not only animal cells, but also other cells, regardless of being of eukaryotic or prokaryotic origin, as long as they can express a reporter gene in a similar system.

Test samples used in the screening include, for example, cell extracts, expression products of a gene library, synthetic low molecular weight compounds, synthetic peptides, naturally occurring compounds, etc. Note that these test compounds are examples and the present invention is not limited thereto.

Compounds isolated by this screening are candidates for a compound that promotes or suppresses the activity of a protein of the present invention (agonist or antagonist). They are also candidates as compounds that inhibit the interaction between the proteins of the present invention and certain molecules that interact with the proteins. These compounds may be possibly applied to the treatment or prevention of diseases related to the proteins of the present invention.

Further, the present invention relates to use of the compounds obtainable by the screening of the present invention for medical purposes. Thus, the present invention relates to the use of an agent comprising a compound obtainable by the aforementioned screening method as a main ingredient, in the treatment and prevention of Alzheimer's disease, or in the regulation of amyloid β protein aggregation. The present invention also relates to a therapeutic and preventive agent comprising such a compound as a main ingredient. Furthermore, compounds obtained by the screening method of the present invention are expected to be related to other amyloidoses, specifically,

schizophrenia and related neuropathies, rheumatoid arthritis ,
tuberculosis, leprosy, bronchitis, SLE, dialysis amyloidosis,
diabetic amyloidosis, atrial amyloidosis, etc., and can be used as
therapeutic and preventive agents for these diseases and for screening
5 such therapeutic and preventive agents.

The proteins, nucleotides, antibodies of the present invention
and the compounds isolated by the above screening mentioned are useful
for regulating amyloid β protein aggregation. When used as
pharmaceutical agents, they themselves can be used as pharmaceutical
10 agents, or they can be formulated for use by any known pharmaceutical
method. For example, the compounds can be formulated by mixing with
pharmacologically acceptable carriers or vehicles, specifically,
sterilized water, physiological saline, plant-oil, emulsifiers,
suspending agents, and used. Methods well known to one skilled in
15 the art may be used to administer a pharmaceutical agent to patients,
for example as intra-arterial, intravenous, percutaneous injections,
and so on. The dosage varies according to the body-weight and age
of the patient, and also the administration method, but one skilled
in the art can suitably select an appropriate dosage. If the compound
20 can be encoded by a polynucleotide, the polynucleotide can be inserted
into a vector for gene therapy to perform the therapy. The dosage
and method of administration vary according to the body-weight, age,
and symptoms of a patient, but one skilled in the art can select them
suitably.

25 The proteins of the present invention are predicted to have other
physiological activities, in addition to the activity of suppressing
or promoting amyloid β protein aggregation. Such activities can be
determined as follows: Since the proteins of the present invention
are secretory or membrane proteins, and their amino acid sequences
30 have been elucidated, it is possible to analyze whether they have
other physiological activities, in addition to the activity of
suppressing or promoting amyloid β protein aggregation, by expressing
recombinants in appropriate expression systems, or by using antibodies
that specifically recognize the proteins.

35 The biological activities of each protein of the present
invention can be analyzed, based on, for example, "Glycobiology" M.

Fukuda and A. Kobata (ed.), 1993; "Growth Factors" I. McKay and I. Leigh (ed.), 1993; and "Extracellular Matrix" M. A. Haralson and J. R. Hassell (ed.), 1995; in "The Practical Approach Series", IRL PRESS, or "Glycoprotein Analysis in Biomedicine" Elizabeth F. Hounsell (ed.), 5 1993; in "Method in Molecular Biology" series, Humana Press. Alternatively, biological activities related to secretory or membrane proteins can be analyzed based on the disclosures found in "Growth and differentiation factors and their receptors", The Japanese Biochemical Society (ed.), Shin-Seikagaku Jikken Kouza Vol.7 , 10 Tokyo-Kagaku-Doujin Co. Ltd, 1991, and in Volume 296 "Neurotransmitter Transporters"; Volume 294 "Ion Channels (Part C)"; Volume 293 "Ion Channels (Part B)", Volume 292 "ABC Transporters"; Volume 288 "Chemokine Receptors"; Volume 287 "Chemokines"; Volume 248 "Proteolytic Enzymes"; Volume 245 "Extracellular Matrix Components"; 15 Volume 244 "Proteolytic Enzymes"; Volume 230 "Guide to Techniques in Glycobiology"; Volume 198 "Peptide Growth Factors"; Volume 192 "Biomembranes"; Volume 191 "Biomembranes"; Volume 149 "Drug and Enzyme Targeting", in "Methods in Enzymology", Academic Press, and so on.

A pharmaceutical agent can be made based on functional analyses 20 using a secretory or membrane protein.

In the case of a membrane protein, it would most likely be a protein having a function as a receptor or ligand by being expressed on the cell surface. Therefore, it is possible to reveal a new ligand-receptor relationship by screening a membrane protein of the 25 invention based on the binding activity with a known ligand or receptor. Screening can be performed according to known methods.

For example, a screening using cells expressing a receptor proteins of the present invention can be performed as follows. Namely, it is possible to screen a receptor capable of binding to a specific 30 protein by using the following steps of: (a) contacting a cell sample with a protein of the invention, or a partial peptide thereof, and (b) selecting a cell that binds to the protein or peptide.

This screening can be conducted, for example, as follows. First, a protein of the invention is expressed, and the recombinant protein 35 is purified. Next, the purified protein is labeled, binding assay is performed using various cell lines or primary cultured cells,

and cells that are expressing a receptor are selected (Growth and differentiation factors and their receptors, Shin-Seikagaku Jikken Kouza Vol.7 (1991) Honjyo, Arai, Taniguchi, and Muramatsu edit, p203-236, Tokyo-Kagaku-Doujin). Protein labeling can be achieved
 5 by labeling with radioisotopes (RI) such as ^{125}I , and by enzymes (alkaline phosphatase etc.) as well. Alternatively, a protein of the invention may be used without labeling, and then detected by using a labeled antibody against the protein. The cells that are selected by the above screening methods, which express a receptor
 10 of a protein of the invention, can be used for further screening agonists or antagonists of the receptor.

Once a receptor of a protein of the invention or the cells expressing the receptor is obtained by screening, it is possible to screen a compound that inhibits the binding between the protein
 15 and its receptor (agonists or antagonists of the receptor, for example) by utilizing the binding ability of the protein to its receptor or cells expressing the receptor.

The screening method comprises the steps of : (a) contacting a protein of the invention with its receptor or cells expressing
 20 the receptor in the presence of a test sample, (b) detecting the binding activity between the protein and its receptor or the cells expressing the receptor, and (c) selecting a compound that can reduce the binding activity compared to the activity in the absence of the sample.

25 Test samples that can be used in the screening include cell extracts, expression products of a gene library, synthesized low molecular compounds, synthesized peptides, and natural compounds, for example, but are not limited thereto. A compound that is isolated by the above screening using the binding ability of a protein of
 30 the invention can be also used as the test sample.

A compound isolated by the screening may be a candidate for an agonist or an antagonist of a receptor of a protein of the invention. By utilizing an assay that monitors a change in intracellular signaling such as phosphorylation, which results from the reduction of the
 35 binding between the protein and its receptor, it is possible to identify whether the obtained compound is an agonist or antagonist of the

receptor. Also, the compound may be a candidate for a molecule that can inhibit the interaction between a protein of the invention and its associating proteins (including receptors). Such compounds can be used for developing drugs for preventing or treating a disease associated with the protein of the invention.

When a protein of the invention is a secretory protein, it may be a factor that can regulate cellular conditions such as growth and differentiation. A novel factor that regulates cellular conditions can be discovered by adding the secretory protein of the invention to a certain kind of cell, and performing screening by utilizing a cellular change in growth or differentiation, or activation of a particular gene.

The screening may be performed, for example, as follows. First, the protein of the invention is expressed and the recombinant protein is purified. Then, the purified protein is added to various kinds of cell lines or primary cultures, and a change in the cell growth and/or differentiation is monitored. Alternatively, the induction of a particular gene that is known to be involved in a certain cellular change can be detected at the level of mRNA expression or protein amount. Alternatively, the amount of an intracellular molecule (low molecular compounds) that is changed by the function of a gene product (protein) that is known to be functioning in a certain cellular change may be used for the detection.

Once the screening reveals that a protein of the invention can regulate cellular conditions or functions, it is possible to apply the protein as a pharmaceutical agent for related diseases by itself or by altering a part of it.

As was described for membrane proteins, secretory proteins provided by the invention may be used to explore a novel ligand-receptor interaction using a screening based on the binding ability to a known ligand or receptor. A similar method can be used to identify an agonist or antagonist. The resulting compounds obtained by the methods can be candidates for compounds that can inhibit the interaction between a protein of the invention and an interacting molecule (including receptors). Such compounds may be used as pharmaceutical agents for preventing and treating diseases, in which the protein may play a

certain role.

If a protein or gene that is affected by the screening turns out to be associated with a disease, it is possible to screen a gene or compound that can regulate its expression and/or activity either
5 directly or indirectly by utilizing a protein of the present invention.

For example, a protein of the invention is expressed and purified as a recombinant protein. Then, the protein or gene that is affected by the screening is purified, and screened by the binding ability. Alternatively, the screening can be performed by adding in advance
10 a compound that is a candidate for an inhibitor, and observing changes in binding. Compounds obtained by such a screening can be used for developing pharmaceutical agents for diseases with which a proteins of the present invention is associated. Similarly, if a regulatory factor obtained by the screening turns out to be a protein, a compound
15 that affects the original expression level and/or activity of the protein can be used for the same purpose described above.

If a secretory or membrane proteins of the present invention has an enzymatic activity, it is possible to identify the activity by adding a compound to the protein under appropriate conditions,
20 and monitoring a change of the compound. It is also possible to screen a compound that inhibits an activity of a protein of the invention by utilizing the activity as an index.

In a screening given as an example, a protein of the invention is expressed and the recombinant protein is purified. Then, a
25 compound is added to the purified protein, and the amount of the compound and the reaction products are examined. Alternatively, a compound that is a candidate for an inhibitor is pretreated, then the compound (substrate) that can react with the purified protein is added, and the amount of the substrate and the reaction products
30 are examined.

The compounds obtained in the screening may be used as pharmaceutical agents for diseases with which a protein of the invention is associated.

Whether or not the secretory or membrane proteins of the present
35 invention is a novel protein associated with a disease is determined using also methods other than those described above. Namely, this

can be done by obtaining a specific antibody against a protein of the invention, and examining the relationship between the expression or activity of the protein and a certain disease. In an alternative way, it may be analyzed referring to methods in "Molecular Diagnosis of Genetic Diseases" (Elles R. edit, (1996) in the series of "Method in Molecular Biology" (Humana Press).

In addition to purifying a protein of the invention, an antibody that binds to a protein of the invention may be used , for example, for testing or diagnosing structural or functional aberrations of the protein of the present invention .

Polynucleotides of the present invention were observed to be aberrantly expressed in the hippocampus of patients with Alzheimer's disease. Therefore, Alzheimer's disease may be detected by measuring the expression of a polynucleotide of the present invention. Thus, the present invention relates to a method for detecting Alzheimer's disease, comprising the following steps of:

- (1) measuring the expression of at least one of the polynucleotides selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 3, SEQ ID NO. 7, and SEQ ID NO. 9,
- (2) comparing the measurement obtained with that obtained when the polynucleotide is expressed in healthy subjects; and,
- (3) linking Alzheimer's disease with said change in expression of the polynucleotide.

In the present invention, an expression state of a polynucleotide can be understood by analyzing any one of the steps in the transcription of the gene into mRNA and in the translation into the protein. More specifically, the state of transcription can be understood by measuring mRNA comprising an aforementioned nucleotide sequence in place of an aforementioned polynucleotide. Any known method, such as Northern hybridization and RT-PCR, can be used to measure mRNA. Alternatively, measurement of a protein having an amino acid sequence encoded by a polynucleotide, or a fragment of the protein, would elucidate the state of translation into the protein. Proteins can be measured by Western blot using antibodies recognizing the proteins and various immunoassays. The testing method of the present invention can be conducted for blood samples and spinal fluid samples, or hippocampal

tissue obtained by an autopsy. To observe the state of expression of the polynucleotides of the present invention, using tissue specimens as samples, analytical methods, such as *in situ* hybridization and immunohistological techniques, may be used. if the state of expression of a polynucleotide of the present invention is analyzed, and if, for example, the expression of PSEC256 is found to be enhanced in the brain of AD patients compared to the expression in normal brains, PSEC256 can be linked to Alzheimer's disease. Also, if inhibition of the expression of PSEC0012, PSEC0220, PSEC0242, or such, is observed, they can also be linked to Alzheimer's disease.

The present invention also relates to a reagent for revealing an expression state of a polynucleotide of the present invention. More specifically, the present invention relates to the use of a polynucleotide comprising at least 15 nucleotides, which is complementary to any one of the polynucleotides of the present invention, or to a complementary strand thereof, for detecting a polynucleotide of the present invention. Alternatively, the present invention relates to the use of an antibody recognizing any one of the proteins of the present invention for detecting the protein.

Best Mode for Implementing the Invention

The present invention shall be described in detail below with reference to examples, but it is not be construed as being limited thereto.

Example 1: Cloning of cDNAs that encode the proteins promoting or preventing aggregation and deposition of amyloid β protein

NT-2 neuron progenitor cells (Stratagene), a teratocarcinoma cell line from human embryo testis, which can differentiate into neurons when treated with retinoic acid, were used. The NT-2 cells were cultured according to the manufacturer's instructions,

(1) without retinoic acid treatment (NT2RM1),

(3) 2 weeks after retinoic acid was added to cultured NT-2 cells (NT2RP3)

The cells were harvested separately, from which mRNA was extracted by the method described in the literature (Molecular Cloning 2nd edition. Sambrook J., Fritsch, E.F., and Maniatis T. (1989) Cold

Spring Harbor Laboratory Press). Poly(A)⁺RNA was further purified from the mRNA using oligo-dT cellulose.

Similarly, human placenta (PLACE1), and brain-enriched tissues from human embryo (HEMBA1) were used to extract mRNA by the method described in the literature (Molecular Cloning 2nd edition. Sambrook J., Fritsch, E.F., and Maniatis T. (1989) Cold Spring Harbor Laboratory Press). Poly(A)⁺RNA was further purified from the mRNA using oligo-dT cellulose.

Each poly(A)⁺RNA was used to construct a cDNA library by the oligo-capping method (Maruyama M. and Sugano S. (1994) Gene 138: 171-174). Using the Oligo-cap linker (agcaucgagu cggccuuguu ggccuacugg/SEQ ID NO: 11) and the Oligo-dT primer (gcggtgaag acggcctatg tggccttttt tttttttttt tt/SEQ ID NO: 12), BAP (Bacterial Alkaline Phosphatase) treatment, TAP (Tobacco Acid Phosphatase) treatment, RNA ligation, the first strand cDNA synthesis, and removal of RNA were performed as described in the reference (Suzuki and Kanno (1996) Protein Nucleic acid and Enzyme. 41: 197-201; Suzuki Y. et al. (1997) Gene 200: 149-156). Next, 5'- and 3'-PCR primers ((agcatcgagt cggccttggt g/SEQ ID NO: 13) and (gcggtgaag acggcctatg t/SEQ ID NO: 14) respectively) were used to perform PCR (polymerase chain reaction) to convert the cDNA into double stranded cDNA, which was then digested with SfiI. Then, the DraIII-cut pUC19FL3 vector (for NT2RM1), or pME18SFL3 (GenBank AB009864, expression vector; for NT2RP3, PLACE1, and HEMBA1) was used for cloning the cDNA in an unidirectional manner, and cDNA libraries were obtained. The clones having an insert cDNA of 1 kb length or shorter were removed for NT2RM1, PLACE1, and HEMBA1, and the clones having an insert of 2 kb or shorter were removed for NT2RP3. Then, the nucleotide sequence of the 5'- and 3'- ends of the cDNA clones was analyzed using DNA sequencing reagents (Dye Terminator Cycle Sequencing FS Ready Reaction Kit, dRhodamine Terminator Cycle Sequencing FS Ready Reaction Kit, or BigDye Terminator Cycle Sequencing FS Ready Reaction Kit, from by PE Biosystems), performing sequencing reactions according to the instructions, and analyzing with a DNA sequencer (ABI PRISM 377, PE Biosystems).

The pME18SFL3 eukaryotic expression vector was used for the

construction of the cDNA libraries, except for NT2RM1. The vector contains SR α promoter and SV40 small t intron in the upstream of the cloning site, and SV40 polyA added signal sequence site in the downstream. As the cloning site has asymmetrical DraIII sites, and
5 cDNA fragments contain a complementary SfiI site on their ends, the cloned cDNA fragments can be inserted downstream of the SR α promoter unidirectionally. Therefore, the plasmid clones containing full-length cDNA can be introduced directly into COS cells to be expressed transiently. Thus, experimental analysis as proteins
10 (gene products) or as biological activities can be very easily carried out.

The fullness ratio of the 5'-end sequence of the cDNA clones in the libraries constructed by the oligo-capping method was determined as follows. For all the clones in which the 5'-end sequence
15 was identical to that of any known human mRNA in the public database, the clones were judged to be "complete/full length", if they had a longer 5'-end sequences than the known human mRNA, or, even if the 5'-end sequence was shorter, if they contained a translation initiation codon. A clone that did not contain a translation
20 initiation codon was judged to be "incomplete/not full length". The fullness ratio ((the number of complete clones)/(the number of complete clones) + (the number of incomplete clones)) of the 5'-end of the cDNA clones from each library was determined by comparing with the known human mRNA (NT2RM1: 69%; NT2RP3: 61%; PLACE1: 68%;
25 HEMBA1: 53%). The result indicates that the fullness ratio of the 5'-end sequence was extremely high.

The relationship between the cDNA libraries and the clones is shown below.

HEMBA1: PSEC0220

30 NT2RM1: PSEC0012

NT2RP3: PSEC0242, PSEC0256

PLACE1: PSEC0129

Furthermore the complete cDNA sequence and the predicted amino acid sequence of the clones thus selected were determined. The final
35 nucleotide sequences were determined by combining the following three methods, and overlapping the nucleotide sequences determined by each

method.

(1) Long read sequencing from both ends of the cDNA inserts using a Licor DNA sequencer (Sequence reactions were performed according to the manual of the Licor sequencer (Aloka), and DNA sequence was determined using the sequencer.)

(2) Nested sequencing by the Primer Island method which utilizes the in vitro integration reaction of AT2 transposon (Devine S.E., and Boeke J.D. (1994) Nucleic Acids Res. 22: 3765-3772) (Clones were obtained using a kit from PE Biosystems, and sequence reactions were performed using the DNA sequencing reagents from the same company, according to the manufacturer's instructions, and DNA sequence was determined using an ABI PRISM 377 sequencer).

(3) Primer walking by the dideoxy terminator method using custom synthesized DNA primers (Sequencing reactions were performed using the DNA sequencing reagents from PE Biosystems and custom synthesized DNA primers according to the manufacturer's instructions. DNA sequence was determined using an ABI PRISM 377 sequencer).

Obtained sequences were subjected to analysis by ATGpr [A. A. Salamov, T. NISHIKAWA, M. B. Swindells, Bioinformatics, 14: 384-390 (1998); <http://www.hri.co.jp/atgpr/>] and PSORT, and also to BLAST search of GenBank and SwissProt. As a result, most clones were predicted to be secretory or membrane proteins that contain a signal sequence at the N-terminus. For PSEC0242 and PSEC0256, no signal sequence was detected, but the presence of a transmembrane helix was identified by SOSUI, predicting that they are membrane proteins. The results of the above analyses suggest that PSEC0012, PSEC0129, and PSEC0220 are secretory or membrane proteins and have signal sequences at their N-termini, which indicates that they are full-length cDNA clones. PSEC0242 and PSEC0256 are membrane proteins and are predicted to be full-length cDNA clones, although they lack a signal sequence. For PSEC242, a signal sequence could be found at the N-terminus, if the translation is initiated from the third ATG. PSEC0242: No.3 ATG, ATGpr1 0.82, SP-Yes, ORF 171-1343 391 aa, Signal peptide 24;

These results are shown below. The data are shown in the following order, subsequent to each clone name. Each data is discriminated by

"/".

Clone name//

Size of cDNA//

Number of amino acid residues composing the predicted amino acid
5 sequence//

Number of ATG counted from the N-terminus//

Maximal ATGpr1 value//

Presence or absence of signal sequences, or prediction of signal
sequence by PSORT, prediction of membrane proteins by MEMSTAT and
10 SOSUI//

Annotation:

PSEC0012//C-NT2RM1000853//1499//183//1//0.82//125/183 (68.3%) aa
identity to fugu putative protein 2 (PUT2).

PSEC0129//C-PLACE1004170//1828//135//1//0.94//1564/1615 (96%) sim
15 ilarity to human chromosome 16q13/21 BAC clone CIT987SK-A-152E5

PSEC0220//C-HEMBA1005301//1584//365//1//0.94//354/365 (96%) aa id
entity to mouse WNT-6 protein precursor; 1084/1310 (82%) similarit
y to mouse Wnt-6 mRNA

PSEC0242//C-NT2RP3000266//3017//401//1//0.90//No & transmembrane/
20 /242/242 (100%) similarity to human Newcastle disease virus induci
ble protein mRNA, partial 3' UTR region; 85/341 (24%) aa identity
to human myosin heavy chain.

PSEC0256//C-NT2RP3003549//3520//612//1//0.89//No & transmembrane/
/97/362 (26%) aa identity to rat cadherin-6 precursor; 1174/1394
25 (84%) similarity to mRNA for KIAA0345.

Example 5: Expression of the proteins promoting or preventing amyloid
β protein aggregation

COS cells (6×10^6 cells/dish) were seeded, and the expression
30 plasmids (10 μg) obtained in Example 1 were added together with 10
μl of LIPOFECTAMINE (Gibco BRL) to transfect the COS7 cells. The
recombinant cells thus created, which expressed the gene of interest
were cultured in D-MEM medium (+10% FCS, Pc. Sm.) for three days.
Supernatant of the cultured medium was collected as a supernatant
35 fraction.

Example 6: Amyloid β aggregation reaction

The supernatants obtained in Example 5 were used to screen for proteins that promote or suppress amyloid β protein aggregation. In principle, the experiments were conducted according to Methods in Enzymology Volume 309 (1999) p 274-284. Instead of A β 40 and A β 42, which are commonly found in vivo, A β 1-28 consisting of 28 amino acid residues from the N-terminus of A β , which is considered to aggregate to a similar extent as A β 40 and A β 42, was used in the experiments. Experiments as shown below were conducted, and as a result, five clones showing augmented promotion or suppression of aggregation were selected from 108 clones. Experiment method and the activities of the five selected clones are shown below.

(Experiment method)

Three microliters of 1 mM A β 1-28 (Bachem) was added to 17 μ l of the culture supernatant obtained in Example 2, and the reaction was initiated by adding 10 μ l of 300 mM sodium acetate buffer (pH 5.2). After 24 hours, 200 μ l of 10 μ M thioflavin-T (in 50mM potassium phosphate) was added to 5 μ l of the reaction sample. A β aggregation was determined by measuring the fluorescence intensity (excitation 450 nm, emission 482 nm). Synthesized A β 40-1 (a peptide having the inverse sequence of A β 40) was added to the control to a concentration of 100 μ M, instead of adding the culture supernatant. The results are shown in the table below. In the table, relative fluorescence intensities are shown, when the fluorescence intensity of the A β 1-28 aggregation resulting from the addition of A β 40-1 is taken to be 100%. Table. 1 Changes of fluorescence intensity due to A β 1-28 aggregates resulting from addition of A β 40-1

Protein	Fluorescence Intensity
PSEC0012 (supernatant containing product expressed from the clone of SEQ ID NO: 1)	24%
PSEC0129 (supernatant containing the product expressed from the clone of SEQ ID NO: 3)	24%
PSEC0220 (supernatant containing the product expressed from the clone of SEQ	250%

ID NO. 5)	
PSEC0242 (supernatant containing the product expressed from the clone of SEQ ID NO. 7)	16%
PSEC0256 (supernatant containing the product expressed from the clone of SEQ ID NO. 9)	460%

The proteins expressed from the clones comprising the polynucleotides of SEQ ID NOs: 1, 3 and 7 in the sequence list prevent aggregation of amyloid β protein, and the proteins expressed from the clones comprising the polynucleotides of SEQ ID NOs: 5 and 9 in the sequence list promote aggregation of amyloid β protein.

Furthermore, deposition of aggregated synthetic A β was confirmed through microscopic observation after staining with Congo red.

Example 6: Gene Expression analysis in patients with Alzheimer's disease

Expression levels of the gene were compared between healthy subjects and patients with Alzheimer's disease. The primers shown below were prepared for each clone, and quantitative PCR was conducted using hippocampal cDNA as template. Hippocampal cDNA from an Alzheimer's disease patient (age 60) (NO. 0550903) and one from a healthy subject (age 28) (NO. 0510069) were purchased from BioChain Institute Inc. and used. Analysis of the expression levels was performed using PE Applied Biosystems PRISM 7700 according to the protocol for quantitative PCR using SYBR Green (P/N 4304965). The four sets of primers used for PCR are as follows:

PSEC012-894F: GTGGATGCGATCTGTCTCTCC (SEQ ID NO. 15)
PSEC012-1049R: TGCAGAAAGGAACACATGCTG (SEQ ID NO. 16)
PSEC129-190F: CTTCCATGCTTCAGCTGTGG (SEQ ID NO. 17)
PSEC129-340R: GCCCTGGTCTGTATACCTGGG (SEQ ID NO. 18)
PSEC242-599F: CTACGACCTGAGCCAGTGCA (SEQ ID NO. 19)
PSEC242-749R: GAGGGCTTGGAGCTGCTGT (SEQ ID NO. 20)
PSEC256-1502F: GCATTCTACGGGCTGGTCC (SEQ ID NO. 21)
PSEC256-1652R: GGGTTGCCTGGTCCGTATT (SEQ ID NO. 22)

The expression level was reduced in the Alzheimer's disease

patient, compared to the healthy subject, to 1/2 for PSEC012, 1/10 for PSEC129, and 1/9 for PSEC242. On the contrary, the expression level of PSEC256 was increased 1.5 folds in the Alzheimer's disease patient.

5

Industrial Applicability

The present invention provides proteins that suppress or promote aggregation and deposition of amyloid- β protein, and polynucleotides encoding the proteins. The proteins of the present invention and the
10 polynucleotides encoding the proteins are useful as pharmaceutical agents for treating and preventing diseases including Alzheimer's disease, and for diagnosing these diseases. Also, the present invention has enabled screening for a compound that suppresses or promotes aggregation of amyloid- β protein. It is hoped that the
15 screening method of the present invention would be used for developing effective therapeutic agents for Alzheimer's disease that prevent amyloid- β aggregation.

CLAIM

1. A polynucleotide encoding a protein that suppresses or promotes the aggregation or deposition of amyloid- β protein, wherein the polynucleotide is selected from the group consisting of:
 - 5 (a) a polynucleotide that comprises a nucleotide sequence as set forth in SEQ ID NO: 1, 3, 5, 7 or 9,
 - (b) a polynucleotide that encodes a protein having a amino acid sequence as set forth in SEQ ID NO: 2, 4, 6, 8 or 10,
 - (c) a polynucleotide that encodes a protein comprising an amino
10 acid sequence in which one or several amino acids of the amino acid sequence of SEQ ID NO. 2, 4, 6, 8 or 10, have been substituted, deleted, inserted and/or added,
 - (d) a polynucleotide that hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence as set forth
15 in SEQ ID NO. 1, 3, 5, 7 or 9; or,
 - (e) a polynucleotide that shows at least (i) 60%, (ii) 70%, (iii) 80%, (iv) 90%, or (v) 95% homology to a nucleotide sequence as set forth in SEQ ID NO. 1, 3, 5, 7 or 9.
2. A polynucleotide encoding a partial peptide of a protein encoded
20 by a polynucleotide according to claim 1.
3. A peptide or protein encoded by a polynucleotide according to claim 1 or 2.
4. A protein that suppresses or promotes the aggregation of amyloid- β protein, wherein said protein is encoded by a polynucleotide that,
25 from a molecular evolutionary aspect, originated from the same gene from which a polynucleotide according to claim 1 originated from.
5. A vector comprising a polynucleotide according to claim 1 or 2.
6. A transfectant harboring a polynucleotide according to claim 1
30 or 2 or the vector according to claim 5.
7. A method for producing the peptide or protein according to claim 3, wherein said method comprises the steps of: culturing the transfectant according to claim 6, and recovering the expression product.
- 35 8. A polynucleotide comprising a polynucleotide according to claim 1 or 2 or a nucleotide sequence complementary to the complementary

strand of a polynucleotide according to claim 1 or 2, wherein said polynucleotide comprises at least 15 nucleotides.

9. An antibody against the peptide or protein according to claim 3.

10. An immunological assay comprising the step of: monitoring an
5 immunological reaction between the peptide or protein according to claim 3 and the antibody according to claim 9.

11. A method of screening for a compound that regulates the activity of a protein encoded by a polynucleotide according to claim 1, wherein said method comprises the following steps of:

10 contacting a candidate compound with a protein encoded by a polynucleotide according to claim 1, or with a cell expressing said protein, in the presence of amyloid- β protein, and, selecting the candidate compound that regulates the aggregation or deposition of amyloid- β protein.

15 12. A method of screening for a compound that regulates expression of a protein encoded by a polynucleotide according to claim 1, wherein said method comprises the following steps of:

(1) contacting a candidate compound with a cell, wherein a vector has been introduced into said cell, said vector comprising:
20 an expression regulatory region of a gene comprising a nucleotide sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, and SEQ ID NO. 9, and, a reporter gene operably linked downstream of the expression regulatory region,

(2) measuring the activity of the reporter gene, and,
(3) selecting the candidate compound that increases or decreases the reporter activity measured in step (b) when compared to the control.

30 13. A pharmaceutical agent comprising a compound obtained by the method according to claim 11 or 12.

14. A pharmaceutical agent comprising the peptide or protein according to claim 3 or 4.

35 15. A pharmaceutical agent comprising an antisense polynucleotide complementary to the protein-coding sequence of a polynucleotide according to claim 1.

16. The pharmaceutical agent according to claim 13 or 14, wherein said pharmaceutical agent is a preventive or therapeutic agent for Alzheimer's disease, and,

17. A method for detecting Alzheimer's disease, comprising the following steps of:

(1) measuring the expression of a polynucleotide according to claim 1,

(2) comparing the measurement obtained by (1) with that obtained when the polynucleotide is expressed in healthy subjects,

(3) linking Alzheimer's disease with said change in expression of the polynucleotide.

ABSTRACT

The present invention provides: proteins suppressing or promoting the aggregation or deposition of amyloid- β protein; polynucleotides encoding the proteins; a method for screening a compound suppressing or promoting the aggregation or deposition of amyloid- β protein; and therapeutic agents for treating or preventing Alzheimer's diseases comprising a compound that regulates the activity of a protein suppressing or promoting the aggregation or deposition of amyloid- β protein.

Japanese Language Declaration (日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名 日付	Third inventor's signature Date
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名 3-00	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名 日付	Fourth inventor's signature Date Yuri Hio May 30, 2002
住所	Residence 4508-19-201, Yana, <u>Kisarazu-shi</u> , Chiba JPX 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名 日付	Fifth inventor's signature Date
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Declaration and Power of Attorney For Patent Application

Japanese Language Declaration

Japanese Language Declaration (日本語宣言書)

私は、米国法典第 35 編 119 条(a) - (d)項又は 365 条 (b) 項に基づき下記の、米国以外の国の少なくとも一カ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

Prior Foreign Application(s)
外国での先行出願

11/194179
(Number)
(番号)

Japan
(Country)
(国名)

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

(Application No.)
(出願番号)

(Filing Date)
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PCT/JP00/04515
(Application No.)
(出願番号)

6 July 2000
(Filing Date)
(出願日)

(Application No.)
(出願番号)

(Filing Date)
(出願日)

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I hereby claim foreign priority under Title 35, United States Code, § 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Priority Claimed
優先権主張

8 July 1999
(Day/Month/Year Filed)
(出願年月日)

☒ ☐
Yes No
はい いいえ

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

60/159,586
(Application No.)
(出願番号)

18 October 1999
(Filing Date)
(出願日)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Pending

(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

[illegible]

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)



Send Correspondence to:



Direct Telephone calls to: (name and telephone number)

(703) 413-3000

Page 3 of 5

Japanese Language Declaration (日本語宣言書)

第六の共同発明者の氏名	5-00	Full name of sixth joint inventor, If any <u>Susumu SATOH</u>
第六の共同発明者の署名	日付	Sixth inventor's signature <i>Susumu Satoh</i> Date <i>April 12, 2002</i>
住所		Residence 6-19-11, Kinunodai, Yawara-mura, <u>Tsukuba-gun</u> , <u>JPX</u> Ibaraki 300-2436, Japan
住所		Citizenship Japan
郵便の宛先		Mailing Address same as above

第三の共同発明者の氏名	6-00	Full name of seventh joint inventor, If any <u>Hiroyuki ARAKAWA</u>
第三の共同発明者の署名	日付	Seventh inventor's signature <i>Hiroyuki Arakawa</i> Date <i>April 12, 2002</i>
住所		Residence 1-22-9, Kannondai, <u>Tsukuba-shi</u> , Ibaraki <u>JPX</u> 305-0856, Japan
住所		Citizenship Japan
郵便の宛先		Mailing Address same as above

第四の共同発明者の氏名	7-00	Full name of eighth joint inventor, If any <u>Masahiko MORITA</u>
第四の共同発明者の署名	日付	Eighth inventor's signature <i>M. Morita</i> Date <i>Apr 17 '02</i>
住所		Residence 1-20-1-2-103, Chuo, <u>Ushiku-shi</u> , Ibaraki 300-1234, <u>JPX</u> Japan
住所		Citizenship Japan
郵便の宛先		Mailing Address same as above

Japanese Language Declaration (日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
第六の共同発明者の署名	Sixth inventor's signature
住所	Residence 6-19-11, Kinunodai, Yawara-mura, Tsukuba-gun, Ibaraki 300-2436, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第三の共同発明者の氏名	Full name of seventh joint inventor, If any Hiroyuki ARAKAWA
第三の共同発明者の署名	Seventh inventor's signature
住所	Residence 1-22-9, Kannondai, Tsukuba-shi, Ibaraki 305-0856, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of eighth joint inventor, If any Masahiko MORITA
第四の共同発明者の署名	Eighth inventor's signature
住所	Residence 1-20-1-2-103, Chuo, Ushiku-shi, Ibaraki 300-1234, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

217925US0XPCT

Declaration and Power of Attorney For Patent Application**特許出願宣言書及び委任状****Japanese Language Declaration****日本語宣言書**

下記の氏名の発明者として、私は以下の通り宣言します。

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

上記発明の明細書は、

☐ 本書に添付されています。

☐ ____ 月 ____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

____ とし、

(該当する場合) ____ に訂正されました。

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

私は、連邦規則法典第 37 編第 1 条 56 項に定義されたとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

the specification of which

☐ is attached hereto.

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration (日本語宣言書)

私は、米国法典第 35 編 119 条(a) - (d)項又は 365 条 (b) 項に基づき下記の、米国以外の国の少なくとも一カ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

Prior Foreign Application(s)
外国での先行出願

<u>11/194179</u> (Number) (番号)	<u>Japan</u> (Country) (国名)
--------------------------------------	-----------------------------------

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

<u> </u> (Application No.) (出願番号)	<u> </u> (Filing Date) (出願日)
--	---

私は、下記の米国法典第 35 編 120 条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約 365 条 (c) に基づく権利をここに主張します。また、本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義された特許資格の有無に関する重要な情報について開示義務があることを認識しています。

<u>PCT/JP00/04515</u> (Application No.) (出願番号)	<u>6 July 2000</u> (Filing Date) (出願日)
--	--

<u> </u> (Application No.) (出願番号)	<u> </u> (Filing Date) (出願日)
--	---

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行えば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby claim foreign priority under Title 35, United States Code, § 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Priority Claimed
優先権主張

<u>8 July 1999</u> (Day/Month/Year Filed) (出願年月日)	<input checked="" type="checkbox"/> <input type="checkbox"/> Yes No はい いいえ
---	--

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

<u>60/159,586</u> (Application No.) (出願番号)	<u>18 October 1999</u> (Filing Date) (出願日)
--	--

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

<u>Pending</u> (Status: Patented, Pending, Abandoned) (現況: 特許許可済、係属中、放棄済)	
---	--

<u> </u> (Status: Patented, Pending, Abandoned) (現況: 特許許可済、係属中、放棄済)	
--	--

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration (日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
(弁護士、または代理人の指名及び登録番号を明記のこと)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)



022850

書類送付先

Send Correspondence to:



022850

直接電話連絡先：(名前及び電話番号)

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名 <div style="text-align: right;">1-00</div>	Full name of sole or first inventor <u>Toshio OTA</u>
発明者の署名 <div style="text-align: right;">日付</div>	Inventor's signature <div style="text-align: right;">Date</div>
住所	Residence c/o Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratories, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan JPX
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

第二の共同発明者の氏名	Full name of second joint inventor, if any Takao ISOgai
第二の共同発明者の署名 <div style="text-align: right;">日付</div>	Second inventor's signature <div style="text-align: right;">Date</div>
住所	Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki 300-0303, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration (日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any Tetsuo NISHIKAWA
第三の共同発明者の署名	Third inventor's signature
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名	Fourth inventor's signature
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI
第五の共同発明者の署名	Fifth inventor's signature
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

[illegible]

第三の共同発明者の氏名	Full name of third joint inventor, if any Tetsuo NISHIKAWA
第三の共同発明者の署名	Third inventor's signature
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, Tokyo 173-0013, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO
第四の共同発明者の署名 日付	Fourth inventor's signature Date
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第五の共同発明者の氏名	Full name of fifth joint inventor, if any Mayako YAMAZAKI
第五の共同発明者の署名	Fifth inventor's signature
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration (日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
第六の共同発明者の署名	Sixth inventor's signature
住所	Residence 6-19-11, Kinunodai, Yawara-mura, Tsukuba-gun, Ibaraki 300-2436, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第三の共同発明者の氏名	Full name of seventh joint inventor, If any Hiroyuki ARAKAWA
第三の共同発明者の署名	Seventh inventor's signature
住所	Residence 1-22-9, Kannondai, Tsukuba-shi, Ibaraki 305-0856, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of eighth joint inventor, If any Masahiko MORITA
第四の共同発明者の署名	Eighth inventor's signature
住所	Residence 1-20-1-2-103, Chuo, Ushiku-shi, Ibaraki 300-1234, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

上記発明の明細書は、

☐ 本書に添付されています。

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

(該当する場合) _____ に訂正されました。

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

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As a below named inventor, I hereby declare that:

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AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

the specification of which

☐ is attached hereto.

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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Prior Foreign Application(s)
外国での先行出願

11/194179
(Number)
(番号)

Japan
(Country)
(国名)

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

(Application No.)
(出願番号)

(Filing Date)
(出願日)

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PCT/JP00/04515
(Application No.)
(出願番号)

6 July 2000
(Filing Date)
(出願日)

(Application No.)
(出願番号)

(Filing Date)
(出願日)

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Priority Claimed
優先権主張

8 July 1999
(Day/Month/Year Filed)
(出願年月日)

☒ ☐
Yes No
はい いいえ

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/159,586
(Application No.)
(出願番号)

18 October 1999
(Filing Date)
(出願日)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Pending

(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration (日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
(弁理士、または代理人の指名及び登録番号を明記のこと)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)



022850

書類送付先

Send Correspondence to:



022850

直接電話連絡先：(名前及び電話番号)

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名	Full name of sole or first inventor Toshio OTA
発明者の署名	Inventor's signature
住所	Residence c/o Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratories, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

第二の共同発明者の氏名	Full name of second joint inventor, If any Takao ISOGAI
第二の共同発明者の署名	Second inventor's signature
住所	Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki 300-0303, Japan
国籍	Citizenship Japan
郵便の宛先	Mailing Address same as above

Japanese Language Declaration (日本語宣言書)

第三の共同発明者の氏名	Full name of third joint inventor, If any <u>Tetsuo NISHIKAWA</u>	
第三の共同発明者の署名	日付	Third inventor's signature <i>Tetsuo Nishikawa</i> Date <i>June 11, 2002</i>
住所	Residence 27-3-403, Hikawa-cho, Itabashi-ku, <u>Tokyo</u> J P X 173-0013, Japan	
住所	Citizenship Japan	
郵便の宛先	Mailing Address same as above	

第四の共同発明者の氏名	Full name of fourth joint inventor, If any Yuri HIO	
第四の共同発明者の署名	日付	Fourth inventor's signature Date
住所	Residence 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, Japan	
住所	Citizenship Japan	
郵便の宛先	Mailing Address same as above	

第五の共同発明者の氏名	Full name of fifth joint inventor, If any Mayako YAMAZAKI	
第五の共同発明者の署名	日付	Fifth inventor's signature Date
住所	Residence 11-9, Hongo 2-chome, Toride-shi, Ibaraki 302-0022, Japan	
住所	Citizenship Japan	
郵便の宛先	Mailing Address same as above	

Japanese Language Declaration (日本語宣言書)

第六の共同発明者の氏名	Full name of sixth joint inventor, If any Susumu SATOH
第六の共同発明者の署名	Sixth inventor's signature
住所	Residence 6-19-11, Kinunodai, Yawara-mura, Tsukuba-gun, Ibaraki 300-2436, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第三の共同発明者の氏名	Full name of seventh joint inventor, If any Hiroyuki ARAKAWA
第三の共同発明者の署名	Seventh inventor's signature
住所	Residence 1-22-9, Kannondai, Tsukuba-shi, Ibaraki 305-0856, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

第四の共同発明者の氏名	Full name of eighth joint inventor, If any Masahiko MORITA
第四の共同発明者の署名	Eighth inventor's signature
住所	Residence 1-20-1-2-103, Chuo, Ushiku-shi, Ibaraki 300-1234, Japan
住所	Citizenship Japan
郵便の宛先	Mailing Address same as above

PTO/PCT Re: 27 JUN 2002

10/030269

DOCKET NO. 217925US0XPCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: Toshio OTA, et al

SERIAL NO. : 10/030,269

FILING DATE : January 8, 2002

FOR: **AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS****DECLARATION OF Yuri HIO**

I, Yuri HIO am the fourth-named inventor of the above-identified application which is the national phase of PCT U.S. Application based on PCT/JP00/04515 filed July 6, 2000.

Subsequent to the filing of the International application, I have married and changed my surname. Specifically, my maiden name in the International application is "KAWAI". My true and correct married name, **Yuri HIO**, has been set forth on the Declaration, Power of Attorney and Petition filed herewith.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 30, 2002

Yuri HIO
Yuri HIO
(Married Name)

Yuri Kawai
Formerly Yuri KAWAI
(Maiden Name)

4508-19-201, Yana, Kisarazu-shi, Chiba, 292-0812, JAPAN

217925US0XPCT

Declaration and Power of Attorney For Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

私の住所、郵便の宛先、国籍は下記の私の氏名の後に記載された通りです。

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者（下記の名称が複数の場合）であると信じています。

上記発明の明細書は、

☐ 本書に添付されています。

☐ _____ 月 _____ 日に提出され、米国出願番号または特許協定条約国際出願番号を

_____ とし、

(該当する場合) _____ に訂正されました。

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

私は、連邦規則法典第 37 編第 1 条 56 項に定義されたとおり、特許資格の有無について重要な情報を開示する義務があることを認めます。

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

AMYLOID- β PROTEIN AGGREGATION-REGULATING FACTORS (as amended)

the specification of which

☐ is attached hereto.

☒ was filed on July 6, 2000

as United States Application Number or PCT International Application Number

PCT/JP00/04515 and was amended on

_____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration (日本語宣言書)

私は、米国法典第 35 編 119 条(a) - (d)項又は 365 条 (b) 項に基づき下記の、米国以外の国の少なくとも一カ国を指定している特許協力条約 365(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している、本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

Prior Foreign Application(s)
外国での先行出願

Priority Claimed
優先権主張

11/194179
(Number)
(番号)

Japan
(Country)
(国名)

8 July 1999
(Day/Month/Year Filed)
(出願年月日)

☒ ☐
Yes No
はい いいえ

私は、第 35 編米国法典 119 条 (e) 項に基づいて下記の米国特許出願規定に記載された権利をここに主張いたします。

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.)
(出願番号)

(Filing Date)
(出願日)

60/159,586
(Application No.)
(出願番号)

18 October 1999
(Filing Date)
(出願日)

私は、下記の米国法典第 35 編 120 条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約 365 条 (c) に基づく権利をここに主張します。また、本出願の各請求範囲の内容が米国法典第 35 編 112 条第 1 項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内または特許協力条約国際提出日までの期間中に入手された、連邦規則法典第 37 編 1 条 56 項で定義された特許資格の有無に関する重要な情報について開示義務があることを認識しています。

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PCT/JP00/04515
(Application No.)
(出願番号)

6 July 2000
(Filing Date)
(出願日)

Pending
(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

(Application No.)
(出願番号)

(Filing Date)
(出願日)

(Status: Patented, Pending, Abandoned)
(現況: 特許許可済、係属中、放棄済)

私は、私自身の知識に基づいて本宣言書中で私が行なう表明が真実であり、かつ私の入手した情報と私の信じていること、さらに故意になされた虚偽の表明及びそれと同等の行為は米国法典第 18 編第 1001 条に基づき、罰金または拘禁、もしくはその両方により処罰されること、そしてそのような故意による虚偽の声明を行なえば、出願した、又は既に許可された特許の有効性が失われることを認識し、よってここに上記のごとく宣誓を致します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration (日本語宣言書)

委任状：私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。
(弁護士、または代理人の指名及び登録番号を明記のこと)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)



022850

書類送付先

Send Correspondence to:



022850

直接電話連絡先：(名前及び電話番号)

Direct Telephone calls to: (name and telephone number)

(703) 413-3000

単独発明者または第一の共同発明者の氏名		Full name of sole or first inventor Toshio OTA	
発明者の署名	日付	Inventor's signature	Date
住所		Residence c/o Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratories, 3-6-6, Asahi-machi, Machida-shi, Tokyo 194-8533, Japan	
国籍		Citizenship Japan	
郵便の宛先		Mailing Address same as above	

第二の共同発明者の氏名		Full name of second joint inventor, If any Takao ISOGAI	
第二の共同発明者の署名	日付	Second inventor's signature	Date
住所		Residence 511-12, Omuro, Ami-machi, Inashiki-gun, Ibaraki 300-0303, Japan	
国籍		Citizenship Japan	
郵便の宛先		Mailing Address same as above	

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Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala Gly Arg Gln Ala Glu

40 45 50

ttg tgc cag gct gag ccg gaa gtg gtg gca gag cta gct cgg ggc gcc
306

Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu Leu Ala Arg Gly Ala

Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly Thr Arg Gly Arg Ala
 295 300 305

tgc aat agc agc gcc ccg gac ctc agc ggc tgc gac ctg ctg tgc tgc
 1074
 Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys Asp Leu Leu Cys Cys
 310 315 320 325

ggc cgc ggg cac cgc cag gag agc gtg cag ctc gaa gag aac tgc ctg
 1122
 Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu Glu Glu Asn Cys Leu
 330 335 340

tgc cgc ttc cac tgg tgc tgc gta gta cag tgc cac cgc tgc cgt gtg
 1170
 Cys Arg Phe His Trp Cys Cys Val Val Gln Cys His Arg Cys Arg Val
 345 350 355

cgc aag gag ctc agc ctc tgc ctg tgaccgcgcg cccggccgct agactgactt
 1224
 Arg Lys Glu Leu Ser Leu Cys Leu
 360 365

cgcgcagcgg tggctcgcac ctgtgggacc tcagggcacc ggcaccgggc gcctctcgcc
 1284

gctcgagccc agcctctccc tgccaaagcc caactcccag ggctctggaa atggtgaggc
 1344

gaggggcttg agaggaacgc ccacccacga aggcccaggg cgccagacgg ccccgaaaag
 1404

gcgctcgggg agcgttttaa ggacactgta caggccctcc ctccccttgg cctctaggag
 1464

gaaacagttt tttagactgg aaaaaagcca gtctaaaggc ctctggatac tgggctcccc
 1524

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 1584

<210> 6
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 <213> Homo sapiens

<400> 6

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Leu Cys Pro Ala His Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro
 20 25 30

Leu Val Met Asp Pro Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala
 35 40 45

Gly Arg Gln Ala Glu Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu
 50 55 60

Leu Ala Arg Gly Ala Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe
 65 70 75 80

Arg Phe Arg Arg Trp Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg
 85 90 95

Ile Leu Gln Gln Asp Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr
 100 105 110

Ala Ala Gly Ala Ser His Ala Val Thr Gln Ala Cys Ser Met Gly Glu
 115 120 125

Leu Leu Gln Cys Gly Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg
 130 135 140

Pro Ser Gly Leu Pro Gly Thr Pro Gly Pro Gly Pro Ala Gly Ser
 145 150 155 160

Pro Glu Gly Ser Ala Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val
 165 170 175

Asp Phe Gly Asp Glu Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys

180					185					190					
Arg	Gly	Arg	Gly	Asp	Ile	Arg	Ala	Leu	Val	Gln	Leu	His	Asn	Asn	Glu
		195					200					205			
Ala	Gly	Arg	Leu	Ala	Val	Arg	Ser	His	Thr	Arg	Thr	Glu	Cys	Lys	Cys
	210					215					220				
His	Gly	Leu	Ser	Gly	Ser	Cys	Ala	Leu	Arg	Thr	Cys	Trp	Gln	Lys	Leu
225						230					235				240
Pro	Pro	Phe	Arg	Glu	Val	Gly	Ala	Arg	Leu	Leu	Glu	Arg	Phe	His	Gly
				245					250					255	
Ala	Ser	Arg	Val	Met	Gly	Thr	Asn	Asp	Gly	Lys	Ala	Leu	Leu	Pro	Ala
			260					265						270	
Val	Arg	Thr	Leu	Lys	Pro	Pro	Gly	Arg	Ala	Asp	Leu	Leu	Tyr	Ala	Ala
		275					280						285		
Asp	Ser	Pro	Asp	Phe	Cys	Ala	Pro	Asn	Arg	Arg	Thr	Gly	Ser	Pro	Gly
	290					295					300				
Thr	Arg	Gly	Arg	Ala	Cys	Asn	Ser	Ser	Ala	Pro	Asp	Leu	Ser	Gly	Cys
305						310					315				320
Asp	Leu	Leu	Cys	Cys	Gly	Arg	Gly	His	Arg	Gln	Glu	Ser	Val	Gln	Leu
				325					330					335	
Glu	Glu	Asn	Cys	Leu	Cys	Arg	Phe	His	Trp	Cys	Cys	Val	Val	Gln	Cys
			340					345					350		
His	Arg	Cys	Arg	Val	Arg	Lys	Glu	Leu	Ser	Leu	Cys	Leu			
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 120

ttctcagcgc tgattttgag atg atg ggc ttg gga aac ggg cgt cgc agc atg
 173

Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met

1

5

10

aag tcg ccg ccc ctc gtg ctg gcc gcc ctg gtg gcc tgc atc atc gtc
 221

Lys Ser Pro Pro Leu Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val

15

20

25

ttg ggc ttc aac tac tgg att gcg agc tcc cgg agc gtg gac ctc cag
 269

Leu Gly Phe Asn Tyr Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln

30

35

40

aca cgg atc atg gag ctg gaa ggc agg gtc cgc agg gcg gct gca gag
 317

Thr Arg Ile Met Glu Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu

45

50

55

aga ggc gcc gtg gag ctg aag aag aac gag ttc cag gga gag ctg gag
 365

Arg Gly Ala Val Glu Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu

60

65

70

75

aag cag cgg gag cag ctt gac aaa atc cag tcc agc cac aac ttc cag
 413

Lys Gln Arg Glu Gln Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln

	80	85	90
ctg gag agc gtc aac aag ctg tac cag gac gaa aag gcg gtt ttg gtg			
461			
Leu Glu Ser Val Asn Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val			
	95	100	105
aat aac atc acc aca ggt gag agg ctc atc cga gtg ctg caa gac cag			
509			
Asn Asn Ile Thr Thr Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln			
	110	115	120
tta aag acc ctg cag agg aat tac ggc agg ctg cag cag gat gtc ctc			
557			
Leu Lys Thr Leu Gln Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu			
	125	130	135
cag ttt cag aag aac cag acc aac ctg gag agg aag ttc tcc tac gac			
605			
Gln Phe Gln Lys Asn Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp			
	140	145	150
140			155
ctg agc cag tgc atc aat cag atg aag gag gtg aag gaa cag tgt gag			
653			
Leu Ser Gln Cys Ile Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu			
	160	165	170
gag cga ata gaa gag gtc acc aaa aag ggg aat gaa gct gta gct tcc			
701			
Glu Arg Ile Glu Glu Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser			
	175	180	185
aga gac ctg agt gaa aac aac gac cag aga cag cag ctc caa gcc ctc			
749			
Arg Asp Leu Ser Glu Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu			
	190	195	200

320	325	330
gag cag gaa gct gcc ggg gaa ggg aga aac cag cag aaa ctg aga gga		
1181		
Glu Gln Glu Ala Ala Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly		
335	340	345
gaa gat gac tac aac atg gat gaa aat gaa gca gaa tct gag aca gac		
1229		
Glu Asp Asp Tyr Asn Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp		
350	355	360
aag caa gca gcc ctg gca ggg aat gac aga aac ata gat gtt ttt aat		
1277		
Lys Gln Ala Ala Leu Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn		
365	370	375
gtt gaa gat cag aaa aga gac acc ata aat tta ctt gat cag cgt gaa		
1325		
Val Glu Asp Gln Lys Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu		
380	385	390
aag cgg aat cat aca ctc tgaattgaac tggaatcaca tatttcacaa		
1373		
Lys Arg Asn His Thr Leu		
400		
cagggccgaa gagatgactt taaaatgttc atgagggact gaatactgaa aactgtgaaa		
1433		
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1493		
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1553		
taaggtgtca caatttttgg tagtaggtat ttcgtgagaa gctcaacacc aaaactggaa		
1613		
catagttctc cttcaagtgt tggcgacagc ggggcttcct gattctggaa tataactttg		

1673

tgtaaattaa cagccaccta tagaagagtc catctgctgt gaaggagaga cagagaactc
1733

tgggttccgt cgtcctgtcc acgtgctgta ccaagtgtctg gtgccagcct gttacctgtt
1793

ctcactgaaa agtctggcta atgctcttgt gtagtcactt ctgattctga caatcaatca
1853

atcaatggcc tagagcactg actgttaaca caaacgtcac tagcaaagta gcaacagctt
1913

taagtctaaa tacaaagctg ttctgtgtga gaatttttta aaaggctact tgtataataa
1973

cccttgatcat ttttaatgta caaaacgcta ttaagtggct tagaatttga acatttgtgg
2033

tctttattta ctttgcttcg tgtgtgggca aagcaacatc ttccctaaat atatattacc
2093

aagaaaagca agaagcagat taggtttttg acaaaaacaaa caggccaaaa gggggctgac
2153

ctggagcaga gcatggtgag aggcaaggca tgagagggca agttttgttg tggacagatc
2213

tgtgcctact ttattactgg agtaaaagaa aacaaagttc attgatgtcg aaggatatat
2273

acagtgttag aaattaggac tgtttagaaa aacaggaata caatggttgt ttttatcata
2333

gtgtacacat ttagcttgtg gtaaagtact cacaaaactg attttaaaat caagttaatg
2393

tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac
2453

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2513

ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
2573

caggatttga gatgctaagg ccccagagat cgtttgaacc aacctctta ttttcagagg
2633

ggaaaatggg gcctagaagt tacagagcat ctagctgggtg cgctggcacc cctggcctca
2693

cacagactcc cgagtagctg ggactacagg cacacagtca ctgaagcagg ccttggttgc
2753

aattcacgct gccacctcca acttaaacad ttttcataat tgatgtcctt agtcactaag
2813

gttaaacttt cccacccaga aaaggcaact tagataaaat cttagagtac tttcatactc
2873

ttctaagtcc ttttccagcc tcactttgag tcttccttgg ggttgatagg aattttctct
2933

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2993

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3017

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<212> PRT
<213> Homo sapiens

<400> 8

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20 25 30

Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln Thr Arg Ile Met Glu
35 40 45

Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu Arg Gly Ala Val Glu
50 55 60

Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu Lys Gln Arg Glu Gln
65 70 75 80

Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln Leu Glu Ser Val Asn
85 90 95

Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val Asn Asn Ile Thr Thr

	100		105		110										
Gly	Glu	Arg	Leu	Ile	Arg	Val	Leu	Gln	Asp	Gln	Leu	Lys	Thr	Leu	Gln
	115						120					125			
Arg	Asn	Tyr	Gly	Arg	Leu	Gln	Gln	Asp	Val	Leu	Gln	Phe	Gln	Lys	Asn
	130					135					140				
Gln	Thr	Asn	Leu	Glu	Arg	Lys	Phe	Ser	Tyr	Asp	Leu	Ser	Gln	Cys	Ile
145					150					155					160
Asn	Gln	Met	Lys	Glu	Val	Lys	Glu	Gln	Cys	Glu	Glu	Arg	Ile	Glu	Glu
				165					170					175	
Val	Thr	Lys	Lys	Gly	Asn	Glu	Ala	Val	Ala	Ser	Arg	Asp	Leu	Ser	Glu
			180					185					190		
Asn	Asn	Asp	Gln	Arg	Gln	Gln	Leu	Gln	Ala	Leu	Ser	Glu	Pro	Gln	Pro
		195					200					205			
Arg	Leu	Gln	Ala	Ala	Gly	Leu	Pro	His	Thr	Glu	Val	Pro	Gln	Gly	Lys
	210					215					220				
Gly	Asn	Val	Leu	Gly	Asn	Ser	Lys	Ser	Gln	Thr	Pro	Ala	Pro	Ser	Ser
225					230					235					240
Glu	Val	Val	Leu	Asp	Ser	Lys	Arg	Gln	Val	Glu	Lys	Glu	Glu	Thr	Asn
				245					250					255	
Glu	Ile	Gln	Val	Val	Asn	Glu	Glu	Pro	Gln	Arg	Asp	Arg	Leu	Pro	Gln
			260					265					270		
Glu	Pro	Gly	Arg	Glu	Gln	Val	Val	Glu	Asp	Arg	Pro	Val	Gly	Gly	Arg
		275					280					285			
Gly	Phe	Gly	Gly	Ala	Gly	Glu	Leu	Gly	Gln	Thr	Pro	Gln	Val	Gln	Ala
	290					295					300				
Ala	Leu	Ser	Val	Ser	Gln	Glu	Asn	Pro	Glu	Met	Glu	Gly	Pro	Glu	Arg

305		310		315		320									
Asp	Gln	Leu	Val	Ile	Pro	Asp	Gly	Gln	Glu	Glu	Glu	Gln	Glu	Ala	Ala
				325					330					335	
Gly	Glu	Gly	Arg	Asn	Gln	Gln	Lys	Leu	Arg	Gly	Glu	Asp	Asp	Tyr	Asn
			340				345					350			
Met	Asp	Glu	Asn	Glu	Ala	Glu	Ser	Glu	Thr	Asp	Lys	Gln	Ala	Ala	Leu
		355					360					365			
Ala	Gly	Asn	Asp	Arg	Asn	Ile	Asp	Val	Phe	Asn	Val	Glu	Asp	Gln	Lys
	370					375					380				
Arg	Asp	Thr	Ile	Asn	Leu	Leu	Asp	Gln	Arg	Glu	Lys	Arg	Asn	His	Thr
385					390					395					400

Leu

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 <213> Homo sapiens

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Met Ala Gly His Ser

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atg gtc ctg gtg gaa att ctg gac gtg aat gac aat gtc cct gaa gta
 102
 Met Val Leu Val Glu Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val

10 15 20

atg gtt act tca ctg tcg ctc cct gtg caa gag gat gct cag gtg ggt
150
Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu Asp Ala Gln Val Gly

25

30

35

acc gtc att gcc ctg att agc gtg tcg gat cgt gac tct gga gcc aat
198
Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg Asp Ser Gly Ala Asn

40

45

50

gga cag gtc atc tgc tca ctg aca cct cat gtt ccc ttc aag ctg gtg
246
Gly Gln Val Ile Cys Ser Leu Thr Pro His Val Pro Phe Lys Leu Val

55

60

65

tcc acc tac aag aat tac tac tcg ttg gtg ctg gac agc gcc ctg gac
294
Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu Asp Ser Ala Leu Asp

70

75

80

85

cgc gag agc gtg tcg gcc tat gag ctg gtg gtg act gcg cgg gat ggg
342
Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val Thr Ala Arg Asp Gly

90

95

100

ggc tcg cct tcg ctg tgg gcc acg gct aga gtg tcc gtg gag gtg gcc
390
Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val Ser Val Glu Val Ala

105

110

115

gac gtg aac gac aat gcg cct gcg ttc gcg cag ccc gag tac aca gtg
438
Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln Pro Glu Tyr Thr Val

120

125

130

ttc gtg aag gag aac aac ccg ccg ggc tgc cac atc ttc acg gtg tcg
486

Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His Ile Phe Thr Val Ser
135 140 145

gca tgg gac gcg gac gcg cag aag aac gcg ctg gtg tcc tac tcg ctg
534
Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu Val Ser Tyr Ser Leu
150 155 160 165

gtg gag cgg cgg gtg ggc gag cac gca ctg tcg agc tac gtg tcg gtg
582
Val Glu Arg Arg Val Gly Glu His Ala Leu Ser Ser Tyr Val Ser Val
170 175 180

cac gcg gag agc ggc aag gtg tac gcg ctg cag ccg cta gac cac gag
630
His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln Pro Leu Asp His Glu
185 190 195

gag ctg gag ctg ctg cag ttc cag gtg agc gcg cgc gac gcc ggc gtg
678
Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala Arg Asp Ala Gly Val
200 205 210

ccg cct ctg ggc agc aac gtg acg ctg cag gtg ttc gtg ctg gac gag
726
Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val Phe Val Leu Asp Glu
215 220 225

aac gac aac gcg ccg gca ctg ctg gcg act ccg gct ggc agc gca gga
774
Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro Ala Gly Ser Ala Gly
230 235 240 245

ggc gca gtt agc gag ttg gta ccg cgg tcg gtg ggt gcg ggc cac gtg
822
Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val Gly Ala Gly His Val
250 255 260

gtg gcg aaa gtg cgc gcg gtg gac gct gac tcc ggc tat aac gct tgg
870
Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp

265

270

275

ctg tcc tac gag ttg caa ccg gcg gcg gtc ggc gcg cac atc ccg ttc
918
Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly Ala His Ile Pro Phe

280

285

290

cac gtg ggg ctg tac act ggc gag atc agc acg aca cgc atc ctg gat
966
His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr Thr Arg Ile Leu Asp

295

300

305

gag gcg gac gct ccg cgc cac cgc ctg ctg gtg ctg gtg aag gac cac
1014
Glu Ala Asp Ala Pro Arg His Arg Leu Leu Val Leu Val Lys Asp His

310

315

320

325

ggt gag ccc gcg ctg acg tcc acg gcc acg gtg ctg gtg tcg ctg gtg
1062
Gly Glu Pro Ala Leu Thr Ser Thr Ala Thr Val Leu Val Ser Leu Val

330

335

340

gag aac ggc cag gcc cca aag acg tcg tcg cgg gcc tca gtg ggc gct
1110
Glu Asn Gly Gln Ala Pro Lys Thr Ser Ser Arg Ala Ser Val Gly Ala

345

350

355

gtg gat ccc gaa gcg gct ctg gtg gat att aac gtg tac ctc atc atc
1158
Val Asp Pro Glu Ala Ala Leu Val Asp Ile Asn Val Tyr Leu Ile Ile

360

365

370

gcc atc tgt gcg gtg tcc agc ctg ctg gtg ctc acg ctg ctg ttg tac

1206
Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu Thr Leu Leu Leu Tyr
375 380 385

act gcg ctg cgt tgc tca gcg ccg ccc acc gtg agc cgg tgc gcg ccg
1254
Thr Ala Leu Arg Cys Ser Ala Pro Pro Thr Val Ser Arg Cys Ala Pro
390 395 400 405

ggc aag ccc acg ctg gtg tgc tcc agc gcc gtg ggg agt tgg tct tac
1302
Gly Lys Pro Thr Leu Val Cys Ser Ser Ala Val Gly Ser Trp Ser Tyr
410 415 420

tcg cag cag agg agg cag agg gtg tgc tct gca gag agc ccg ccc aag
1350
Ser Gln Gln Arg Arg Gln Arg Val Cys Ser Ala Glu Ser Pro Pro Lys
425 430 435

acg gac ctc atg gcc ttc agc cca agc ctt cag ctg tct cga gaa gat
1398
Thr Asp Leu Met Ala Phe Ser Pro Ser Leu Gln Leu Ser Arg Glu Asp
440 445 450

tgt tta aat cct ccc agt gaa cca cga cag ccc aac cct gac tgg cgt
1446
Cys Leu Asn Pro Pro Ser Glu Pro Arg Gln Pro Asn Pro Asp Trp Arg
455 460 465

tac tct gcc tcc ctg aga gca ggc atg cac agc tct gtg cac cta gag
1494
Tyr Ser Ala Ser Leu Arg Ala Gly Met His Ser Ser Val His Leu Glu
470 475 480 485

gag gct ggc att cta cgg gct ggt cca gga ggg cct gat cag cag tgg
1542
Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly Pro Asp Gln Gln Trp

490	495	500
cca aca gta tcc agt gca aca cca gaa cca gag gca gga gaa gtg tcc		
1590		
Pro Thr Val Ser Ser Ala Thr Pro Glu Pro Glu Ala Gly Glu Val Ser		
505	510	515
cct cca gtc ggt gcg ggt gtc aac agc aac agc tgg acc ttt aaa tac		
1638		
Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser Trp Thr Phe Lys Tyr		
520	525	530
gga cca ggc aac ccc aaa caa tcc ggt ccc ggt gag ttg ccc gac aaa		
1686		
Gly Pro Gly Asn Pro Lys Gln Ser Gly Pro Gly Glu Leu Pro Asp Lys		
535	540	545
ttc att atc cca gga tct cct gca atc atc tcc atc cgg cag gag cct		
1734		
Phe Ile Ile Pro Gly Ser Pro Ala Ile Ile Ser Ile Arg Gln Glu Pro		
550	555	560
act aac agc caa att gac aaa agt gac ttc ata acc ttc ggc aaa aag		
1782		
Thr Asn Ser Gln Ile Asp Lys Ser Asp Phe Ile Thr Phe Gly Lys Lys		
570	575	580
gag gag acc aag aaa aag aag aaa aag aag aag ggt aac aag acc cag		
1830		
Glu Glu Thr Lys Lys Lys Lys Lys Lys Lys Lys Gly Asn Lys Thr Gln		
585	590	595
gag aaa aaa gag aaa ggg aac agc acg act gac aac agt gac cag		
1875		
Glu Lys Lys Glu Lys Gly Asn Ser Thr Thr Asp Asn Ser Asp Gln		
600	605	610

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1935

ccatgtagca attccctgct cctttttcct atctacatga gccctcttag agacctcaga
1995

aatctgcaga aagttccctg tgtctgtcta gaacgcattt aacaggtttt gtcgtaaaaag
2055

ctttactaag tctgggtgta actctttctc tccactctgg cttgttttca gaacctaaaa
2115

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2235

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2295

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2355

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2415

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2475

ctaggagaca aaactacccc cactgacaag gctttaggag accctaaagt ctgttggctg
2535

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2595

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35 40 45

Asp Ser Gly Ala Asn Gly Gln Val Ile Cys Ser Leu Thr Pro His Val
50 55 60

Pro Phe Lys Leu Val Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu
65 70 75 80

Asp Ser Ala Leu Asp Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val
85 90 95

Thr Ala Arg Asp Gly Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val
100 105 110

Ser Val Glu Val Ala Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln
115 120 125

Pro Glu Tyr Thr Val Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His
130 135 140

Ile Phe Thr Val Ser Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu
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Val Ser Tyr Ser Leu Val Glu Arg Arg Val Gly Glu His Ala Leu Ser
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Ser Tyr Val Ser Val His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln
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Pro Leu Asp His Glu Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala
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Arg Asp Ala Gly Val Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val
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305 310 315 320

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Ser Val His Leu Glu Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly
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Ala Gly Glu Val Ser Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser
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Trp Thr Phe Lys Tyr Gly Pro Gly Asn Pro Lys Gln Ser Gly Pro Gly
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Cys Pro Pro Tyr Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val	
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Ser Gln Lys Asp Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val	
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Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val	
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Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ser	
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Leu Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala	
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Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe
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 Asp Arg His Lys Met Leu Ser
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Cys Pro Pro Tyr Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val
35 40 45

Ser Gln Lys Asp Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val
50 55 60

Pro Gly His Asp Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr
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Glu Glu Arg Ser Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu
85 90 95

Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val
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Asp Pro Leu Ile Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn
115 120 125

Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser
130 135 140

Leu Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala
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Met Ala Ala Ala Ala Val Ser Gly Ala Leu

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Gly Arg Ala Gly Trp Arg Leu Leu Gln Leu Arg Cys Leu Pro Val Ala

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cgt tgc cga caa gcc ctg gtg ccg cgt gcc ttc cat gct tca gct gtg 208

Arg Cys Arg Gln Ala Leu Val Pro Arg Ala Phe His Ala Ser Ala Val

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ggg cta agg tct tca gat gag cag aag cag cag cct ccc aac tca ttt 256

Gly Leu Arg Ser Ser Asp Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe

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Ser Gln Gln His Ser Glu Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu

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Ser Ser His Ser Pro Pro Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu			
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Glu Asp Tyr Glu Ser Glu Glu Gln Leu Gln His Arg Ile Leu Thr Ala			
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gcc ctt gag ttt gtg ccc gcc cac ggg tgg aca gca gag gcg att gca	448		
Ala Leu Glu Phe Val Pro Ala His Gly Trp Thr Ala Glu Ala Ile Ala			
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Glu Gly Ala Gln Val Cys Ile Gly Glu Gly Gly Ala Thr			
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35 40 45

Glu Gln Lys Gln Gln Pro Pro Asn Ser Phe Ser Gln Gln His Ser Glu
50 55 60

Thr Gln Gly Ala Glu Lys Pro Asp Pro Glu Ser Ser His Ser Pro Pro
65 70 75 80

Arg Tyr Thr Asp Gln Gly Gly Glu Glu Glu Glu Asp Tyr Glu Ser Glu
85 90 95

Glu Gln Leu Gln His Arg Ile Leu Thr Ala Ala Leu Glu Phe Val Pro
100 105 110

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Met Leu Pro Pro Leu	
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ccc tcc cgc ctc ggg ctg ctg ctg ctg ctg ctc ctg tgc ccg gcg cac	162
Pro Ser Arg Leu Gly Leu Leu Leu Leu Leu Leu Cys Pro Ala His	
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gtc ggc gga ctg tgg tgg gct gtg ggc agc ccc ttg gtt atg gac cct	210
Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro Leu Val Met Asp Pro	
25 30 35	
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Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala Gly Arg Gln Ala Glu	
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ttg tgc cag gct gag ccg gaa gtg gtg gca gag cta gct cgg ggc gcc	306
Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu Leu Ala Arg Gly Ala	
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Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe Arg Phe Arg Arg Trp	
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Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg Ile Leu Gln Gln Asp	
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His Ala Val Thr Gln Ala Cys Ser Met Gly Glu Leu Leu Gln Cys Gly	
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Ser	Cys	Ala	Leu	Arg	Thr	Cys	Trp	Gln	Lys	Leu	Pro	Pro	Phe	Arg	Glu	
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Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys Asp Leu Leu Cys Cys			
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Cys Arg Phe His Trp Cys Cys Val Val Gln Cys His Arg Cys Arg Val			
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Arg Lys Glu Leu Ser Leu Cys Leu			
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<210> 6

<211> 365

<212> PRT

<213> Homo sapiens

<400> 6

Met Leu Pro Pro Leu Pro Ser Arg Leu Gly Leu Leu Leu Leu Leu Leu
 1 5 10 15

Leu Cys Pro Ala His Val Gly Gly Leu Trp Trp Ala Val Gly Ser Pro
 20 25 30

Leu Val Met Asp Pro Thr Ser Ile Cys Arg Lys Ala Arg Arg Leu Ala
 35 40 45

Gly Arg Gln Ala Glu Leu Cys Gln Ala Glu Pro Glu Val Val Ala Glu
 50 55 60

Leu Ala Arg Gly Ala Arg Leu Gly Val Arg Glu Cys Gln Phe Gln Phe
 65 70 75 80

Arg Phe Arg Arg Trp Asn Cys Ser Ser His Ser Lys Ala Phe Gly Arg
 85 90 95

Ile Leu Gln Gln Asp Ile Arg Glu Thr Ala Phe Val Phe Ala Ile Thr
 100 105 110

Ala Ala Gly Ala Ser His Ala Val Thr Gln Ala Cys Ser Met Gly Glu
 115 120 125

Leu Leu Gln Cys Gly Cys Gln Ala Pro Arg Trp Arg Ala Pro Pro Arg
 130 135 140

Pro Ser Gly Leu Pro Gly Thr Pro Gly Pro Pro Gly Pro Ala Gly Ser
 145 150 155 160

Pro Glu Gly Ser Ala Ala Trp Glu Trp Gly Gly Cys Gly Asp Asp Val
 165 170 175

Asp Phe Gly Asp Glu Lys Ser Arg Leu Phe Met Asp Ala Arg His Lys
 180 185 190

Arg Gly Arg Gly Asp Ile Arg Ala Leu Val Gln Leu His Asn Asn Glu
 195 200 205

Ala Gly Arg Leu Ala Val Arg Ser His Thr Arg Thr Glu Cys Lys Cys
 210 215 220

His Gly Leu Ser Gly Ser Cys Ala Leu Arg Thr Cys Trp Gln Lys Leu
 225 230 235 240

Pro Pro Phe Arg Glu Val Gly Ala Arg Leu Leu Glu Arg Phe His Gly
 245 250 255

Ala Ser Arg Val Met Gly Thr Asn Asp Gly Lys Ala Leu Leu Pro Ala
 260 265 270

Val Arg Thr Leu Lys Pro Pro Gly Arg Ala Asp Leu Leu Tyr Ala Ala
 275 280 285

Asp Ser Pro Asp Phe Cys Ala Pro Asn Arg Arg Thr Gly Ser Pro Gly
 290 295 300

Thr Arg Gly Arg Ala Cys Asn Ser Ser Ala Pro Asp Leu Ser Gly Cys
 305 310 315 320

Asp Leu Leu Cys Cys Gly Arg Gly His Arg Gln Glu Ser Val Gln Leu
 325 330 335

Glu Glu Asn Cys Leu Cys Arg Phe His Trp Cys Cys Val Val Gln Cys
 340 345 350

His Arg Cys Arg Val Arg Lys Glu Leu Ser Leu Cys Leu
 355 360 365

<210> 7
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 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (141)..(1343)

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 ttctcagcgc tgattttgag atg atg ggc ttg gga aac ggg cgt cgc agc atg 173
 Met Met Gly Leu Gly Asn Gly Arg Arg Ser Met
 1 5 10
 aag tcg ccg ccc ctc gtg ctg gcc gcc ctg gtg gcc tgc atc atc gtc 221
 Lys Ser Pro Pro Leu Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val
 15 20 25
 ttg ggc ttc aac tac tgg att gcg agc tcc cgg agc gtg gac ctc cag 269
 Leu Gly Phe Asn Tyr Trp Ile Ala Ser Ser Arg Ser Val Asp Leu Gln
 30 35 40
 aca cgg atc atg gag ctg gaa ggc agg gtc cgc agg gcg gct gca gag 317
 Thr Arg Ile Met Glu Leu Glu Gly Arg Val Arg Arg Ala Ala Ala Glu
 45 50 55
 aga ggc gcc gtg gag ctg aag aag aac gag ttc cag gga gag ctg gag 365
 Arg Gly Ala Val Glu Leu Lys Lys Asn Glu Phe Gln Gly Glu Leu Glu
 60 65 70 75
 aag cag cgg gag cag ctt gac aaa atc cag tcc agc cac aac ttc cag 413
 Lys Gln Arg Glu Gln Leu Asp Lys Ile Gln Ser Ser His Asn Phe Gln
 80 85 90

ctg gag agc gtc aac aag ctg tac cag gac gaa aag gcg gtt ttg gtg	461
Leu Glu Ser Val Asn Lys Leu Tyr Gln Asp Glu Lys Ala Val Leu Val	
95 100 105	
aat aac atc acc aca ggt gag agg ctc atc cga gtg ctg caa gac cag	509
Asn Asn Ile Thr Thr Gly Glu Arg Leu Ile Arg Val Leu Gln Asp Gln	
110 115 120	
tta aag acc ctg cag agg aat tac ggc agg ctg cag cag gat gtc ctc	557
Leu Lys Thr Leu Gln Arg Asn Tyr Gly Arg Leu Gln Gln Asp Val Leu	
125 130 135	
cag ttt cag aag aac cag acc aac ctg gag agg aag ttc tcc tac gac	605
Gln Phe Gln Lys Asn Gln Thr Asn Leu Glu Arg Lys Phe Ser Tyr Asp	
140 145 150 155	
ctg agc cag tgc atc aat cag atg aag gag gtg aag gaa cag tgt gag	653
Leu Ser Gln Cys Ile Asn Gln Met Lys Glu Val Lys Glu Gln Cys Glu	
160 165 170	
gag cga ata gaa gag gtc acc aaa aag ggg aat gaa gct gta gct tcc	701
Glu Arg Ile Glu Glu Val Thr Lys Lys Gly Asn Glu Ala Val Ala Ser	
175 180 185	
aga gac ctg agt gaa aac aac gac cag aga cag cag ctc caa gcc ctc	749
Arg Asp Leu Ser Glu Asn Asn Asp Gln Arg Gln Gln Leu Gln Ala Leu	
190 195 200	
agt gag cct cag ccc agg ctg cag gca gca ggc ctg cca cac aca gag	797
Ser Glu Pro Gln Pro Arg Leu Gln Ala Ala Gly Leu Pro His Thr Glu	
205 210 215	
gtg cca caa ggg aag gga aac gtg ctt ggt aac agc aag tcc cag aca	845
Val Pro Gln Gly Lys Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr	
220 225 230 235	

cca gcc ccc agt tcc gaa gtg gtt ttg gat tca aag aga caa gtt gag	893
Pro Ala Pro Ser Ser Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu	
240 245 250	
aaa gag gaa acc aat gag atc cag gtg gtg aat gag gag cct cag agg	941
Lys Glu Glu Thr Asn Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg	
255 260 265	
gac agg ctg ccg cag gag cca ggc cgg gag cag gtg gtg gaa gac aga	989
Asp Arg Leu Pro Gln Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg	
270 275 280	
cct gta ggt gga aga ggc ttc ggg gga gcc gga gaa ctg ggc cag acc	1037
Pro Val Gly Gly Arg Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr	
285 290 295	
cca cag gtg cag gct gcc ctg tca gtg agc cag gaa aat cca gag atg	1085
Pro Gln Val Gln Ala Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met	
300 305 310 315	
gag ggc cct gag cga gac cag ctt gtc atc ccc gac gga cag gag gag	1133
Glu Gly Pro Glu Arg Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu	
320 325 330	
gag cag gaa gct gcc ggg gaa ggg aga aac cag cag aaa ctg aga gga	1181
Glu Gln Glu Ala Ala Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly	
335 340 345	
gaa gat gac tac aac atg gat gaa aat gaa gca gaa tct gag aca gac	1229
Glu Asp Asp Tyr Asn Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp	
350 355 360	
aag caa gca gcc ctg gca ggg aat gac aga aac ata gat gtt ttt aat	1277
Lys Gln Ala Ala Leu Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn	
365 370 375	
gtt gaa gat cag aaa aga gac acc ata aat tta ctt gat cag cgt gaa	1325

Val Glu Asp Gln Lys Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu
 380 385 390 395

aag cgg aat cat aca ctc tgaattgaac tggaatcaca tatttcacaa 1373
 Lys Arg Asn His Thr Leu
 400

cagggccgaa gagatgactt taaaatgttc atgagggact gaatactgaa aactgtgaaa 1433

tgactaaat aaaatgtaca tctgaagatg attattgtga aattttagta tgcactttgt 1493

gtaggaaaa atggaatggt cttttaaaca gcttttgggg ggtactttgg aagtgtotaa 1553

taagggtgtca caatttttgg tagtaggtat ttcgtgagaa gctcaacacc aaaactggaa 1613

catagttctc cttcaagtgt tggcgacagc ggggcttcct gattctggaa tataactttg 1673

tgtaaattaa cagccaccta tagaagagtc catctgctgt gaaggagaga cagagaactc 1733

tgggttcgt cgtcctgtcc acgtgctgta ccaagtgtg gtgccagcct gttacctgtt 1793

ctcactgaaa agtctggcta atgctcttgt gtagtcactt ctgattctga caatcaatca 1853

atcaatggcc tagagcactg actgttaaca caaacgtcac tagcaaagta gcaacagctt 1913

taagtctaaa tacaaagctg ttctgtgtga gaatttttta aaaggctact tgtataataa 1973

cccttgtcat ttttaatgta caaaacgcta ttaagtggt tagaatttga acatttgttg 2033

tctttattta ctttgcttcg tgtgtgggca aagcaacatc ttccctaaat atatattacc 2093

aagaaaagca agaagcagat taggtttttg acaaaaacaaa caggccaaaa gggggctgac 2153

ctggagcaga gcatggtgag aggcaaggca tgagagggca agttttgttg tggacagatc 2213

tgtgcctact ttattactgg agtaaaagaa aacaaaagttc attgatgtcg aaggatatat 2273

acagtgttag aaattaggac tgtttagaaa aacaggaata caatggttgt ttttatcata 2333
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 ggaaaatggg gcctagaagt tacagagcat ctagctgggtg cgctggcacc cctggcctca 2693
 cacagactcc cgagtagctg ggactacagg cacacagtca ctgaagcagg ccctgtttgc 2753
 aattcacgct gccacctcca acttaaacad tttcataatg tgatgtcctt agtcactaag 2813
 gttaaacttt cccacccaga aaaggcaact tagataaaat cttagagtac tttcatactc 2873
 ttctaagtcc tcttcagcc tcactttgag tcttcttgg ggttgatagg aattttctct 2933
 tgctttctca ataaagtctc tattcatctc atgtttaatt tgtacgcata gaattgctga 2993
 gaaataaaat gtctgttca actt 3017

<210> 8

<211> 401

<212> PRT

<213> Homo sapiens

<400> 8

Met	Met	Gly	Leu	Gly	Asn	Gly	Arg	Arg	Ser	Met	Lys	Ser	Pro	Pro	Leu
1				5					10					15	

Val Leu Ala Ala Leu Val Ala Cys Ile Ile Val Leu Gly Phe Asn Tyr

Trial	Control (n = 10)	MCI (n = 10)	AD (n = 10)
1	95	85	75
2	95	85	75
3	95	80	70
4	95	75	65
5	95	75	65

Gly Asn Val Leu Gly Asn Ser Lys Ser Gln Thr Pro Ala Pro Ser Ser
225 230 235 240

Glu Val Val Leu Asp Ser Lys Arg Gln Val Glu Lys Glu Glu Thr Asn
245 250 255

Glu Ile Gln Val Val Asn Glu Glu Pro Gln Arg Asp Arg Leu Pro Gln
260 265 270

Glu Pro Gly Arg Glu Gln Val Val Glu Asp Arg Pro Val Gly Gly Arg
275 280 285

Gly Phe Gly Gly Ala Gly Glu Leu Gly Gln Thr Pro Gln Val Gln Ala
290 295 300

Ala Leu Ser Val Ser Gln Glu Asn Pro Glu Met Glu Gly Pro Glu Arg
305 310 315 320

Asp Gln Leu Val Ile Pro Asp Gly Gln Glu Glu Glu Gln Glu Ala Ala
325 330 335

Gly Glu Gly Arg Asn Gln Gln Lys Leu Arg Gly Glu Asp Asp Tyr Asn
340 345 350

Met Asp Glu Asn Glu Ala Glu Ser Glu Thr Asp Lys Gln Ala Ala Leu
355 360 365

Ala Gly Asn Asp Arg Asn Ile Asp Val Phe Asn Val Glu Asp Gln Lys
370 375 380

Arg Asp Thr Ile Asn Leu Leu Asp Gln Arg Glu Lys Arg Asn His Thr
385 390 395 400

Leu

<210> 9
 <211> 3520
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (40)..(1875)

<400> 9
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 Met Ala Gly His Ser
 1 5

atg gtc ctg gtg gaa att ctg gac gtg aat gac aat gtc cct gaa gta 102
 Met Val Leu Val Glu Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val
 10 15 20

atg gtt act tca ctg tcg ctc cct gtg caa gag gat gct cag gtg ggt 150
 Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu Asp Ala Gln Val Gly
 25 30 35

acc gtc att gcc ctg att agc gtg tcg gat cgt gac tct gga gcc aat 198
 Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg Asp Ser Gly Ala Asn
 40 45 50

gga cag gtc atc tgc tca ctg aca cct cat gtt ccc ttc aag ctg gtg 246
 Gly Gln Val Ile Cys Ser Leu Thr Pro His Val Pro Phe Lys Leu Val
 55 60 65

tcc acc tac aag aat tac tac tcg ttg gtg ctg gac agc gcc ctg gac 294
 Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu Asp Ser Ala Leu Asp
 70 75 80 85

cgc gag agc gtg tcg gcc tat gag ctg gtg gtg act gcg cgg gat ggg 342
 Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val Thr Ala Arg Asp Gly

90	95	100	
ggc tgc cct tgc ctg tgg gcc acg gct aga gtg tcc gtg gag gtg gcc			390
Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val Ser Val Glu Val Ala			
105	110	115	
gac gtg aac gac aat gcg cct gcg ttc gcg cag ccc gag tac aca gtg			438
Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln Pro Glu Tyr Thr Val			
120	125	130	
ttc gtg aag gag aac aac ccg ccg ggc tgc cac atc ttc acg gtg tgc			486
Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His Ile Phe Thr Val Ser			
135	140	145	
gca tgg gac gcg gac gcg cag aag aac gcg ctg gtg tcc tac tgc ctg			534
Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu Val Ser Tyr Ser Leu			
150	155	160	165
gtg gag cgg cgg gtg ggc gag cac gca ctg tgc agc tac gtg tgc gtg			582
Val Glu Arg Arg Val Gly Glu His Ala Leu Ser Ser Tyr Val Ser Val			
170	175	180	
cac gcg gag agc ggc aag gtg tac gcg ctg cag ccg cta gac cac gag			630
His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln Pro Leu Asp His Glu			
185	190	195	
gag ctg gag ctg ctg cag ttc cag gtg agc gcg cgc gac gcc ggc gtg			678
Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala Arg Asp Ala Gly Val			
200	205	210	
ccg cct ctg ggc agc aac gtg acg ctg cag gtg ttc gtg ctg gac gag			726
Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val Phe Val Leu Asp Glu			
215	220	225	
aac gac aac gcg ccg gca ctg ctg gcg act ccg gct ggc agc gca gga			774
Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro Ala Gly Ser Ala Gly			
230	235	240	245

ggc gca gtt agc gag ttg gta ccg cgg tcg gtg ggt gcg ggc cac gtg	822
Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val Gly Ala Gly His Val	
250 255 260	
gtg gcg aaa gtg cgc gcg gtg gac gct gac tcc ggc tat aac gct tgg	870
Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp	
265 270 275	
ctg tcc tac gag ttg caa ccg gcg gcg gtc ggc gcg cac atc ccg ttc	918
Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly Ala His Ile Pro Phe	
280 285 290	
cac gtg ggg ctg tac act ggc gag atc agc acg aca cgc atc ctg gat	966
His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr Thr Arg Ile Leu Asp	
295 300 305	
gag gcg gac gct ccg cgc cac cgc ctg ctg gtg ctg gtg aag gac cac	1014
Glu Ala Asp Ala Pro Arg His Arg Leu Leu Val Leu Val Lys Asp His	
310 315 320 325	
ggt gag ccc gcg ctg acg tcc acg gcc acg gtg ctg gtg tcc ctg gtg	1062
Gly Glu Pro Ala Leu Thr Ser Thr Ala Thr Val Leu Val Ser Leu Val	
330 335 340	
gag aac ggc cag gcc cca aag acg tcc tcc cgg gcc tca gtg ggc gct	1110
Glu Asn Gly Gln Ala Pro Lys Thr Ser Ser Arg Ala Ser Val Gly Ala	
345 350 355	
gtg gat ccc gaa gcg gct ctg gtg gat att aac gtg tac ctc atc atc	1158
Val Asp Pro Glu Ala Ala Leu Val Asp Ile Asn Val Tyr Leu Ile Ile	
360 365 370	
gcc atc tgt gcg gtg tcc agc ctg ctg gtg ctc acg ctg ctg ttg tac	1206
Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu Thr Leu Leu Leu Tyr	
375 380 385	

act gcg ctg cgt tgc tca gcg ccg ccc acc gtg agc cgg tgc gcg ccg 1254
 Thr Ala Leu Arg Cys Ser Ala Pro Pro Thr Val Ser Arg Cys Ala Pro
 390 395 400 405

ggc aag ccc acg ctg gtg tgc tcc agc gcc gtg ggg agt tgg tct tac 1302
 Gly Lys Pro Thr Leu Val Cys Ser Ser Ala Val Gly Ser Trp Ser Tyr
 410 415 420

tcg cag cag agg agg cag agg gtg tgc tct gca gag agc ccg ccc aag 1350
 Ser Gln Gln Arg Arg Gln Arg Val Cys Ser Ala Glu Ser Pro Pro Lys
 425 430 435

acg gac ctc atg gcc ttc agc cca agc ctt cag ctg tct cga gaa gat 1398
 Thr Asp Leu Met Ala Phe Ser Pro Ser Leu Gln Leu Ser Arg Glu Asp
 440 445 450

tgt tta aat cct ccc agt gaa cca cga cag ccc aac cct gac tgg cgt 1446
 Cys Leu Asn Pro Pro Ser Glu Pro Arg Gln Pro Asn Pro Asp Trp Arg
 455 460 465

tac tct gcc tcc ctg aga gca ggc atg cac agc tct gtg cac cta gag 1494
 Tyr Ser Ala Ser Leu Arg Ala Gly Met His Ser Ser Val His Leu Glu
 470 475 480 485

gag gct ggc att cta cgg gct ggt cca gga ggg cct gat cag cag tgg 1542
 Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly Pro Asp Gln Gln Trp
 490 495 500

cca aca gta tcc agt gca aca cca gaa cca gag gca gga gaa gtg tcc 1590
 Pro Thr Val Ser Ser Ala Thr Pro Glu Pro Glu Ala Gly Glu Val Ser
 505 510 515

cct cca gtc ggt gcg ggt gtc aac agc aac agc tgg acc ttt aaa tac 1638
 Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser Trp Thr Phe Lys Tyr
 520 525 530

gga cca ggc aac ccc aaa caa tcc ggt ccc ggt gag ttg ccc gac aaa 1686

Gly	Pro	Gly	Asn	Pro	Lys	Gln	Ser	Gly	Pro	Gly	Glu	Leu	Pro	Asp	Lys	
535						540					545					
ttc att atc cca gga tct cct gca atc atc tcc atc cgg cag gag cct																1734
Phe Ile Ile Pro Gly Ser Pro Ala Ile Ile Ser Ile Arg Gln Glu Pro																
550						555					560				565	
act aac agc caa att gac aaa agt gac ttc ata acc ttc ggc aaa aag																1782
Thr Asn Ser Gln Ile Asp Lys Ser Asp Phe Ile Thr Phe Gly Lys Lys																
						570					575				580	
gag gag acc aag aaa aag aag aaa aag aag aag ggt aac aag acc cag																1830
Glu Glu Thr Lys Lys Lys Lys Lys Lys Lys Lys Gly Asn Lys Thr Gln																
						585					590				595	
gag aaa aaa gag aaa ggg aac agc acg act gac aac agt gac cag																1875
Glu Lys Lys Glu Lys Gly Asn Ser Thr Thr Asp Asn Ser Asp Gln																
						600					605				610	
tgaggctctc aaatggaaac aagccactta gccagttttt gtaataatgg caaatctctc																1935
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ctttactaag tctggigtta actctttctc tccactctgg cttgttttca gaacctaaaa																2115
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agagaaccac cctgggaaac agaagcagat ctgatgtgtt tcctatacat gtctgtgtct 2655
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gatttattta aaaaaagaga aagtctatag ctataaatct ttaaagagaa atatgaatac 2835
aattccccta aactctctc aaaagagaat tcagtctaca gccatttaaa tgatcattgc 2895
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cacagtaaaa tttcttttctt aaatc 3520

<210> 10

<211> 612

<212> PRT

<213> Homo sapiens

<400> 10

Met Ala Gly His Ser Met Val Leu Val Glu Ile Leu Asp Val Asn Asp
1 5 10 15

Asn Val Pro Glu Val Met Val Thr Ser Leu Ser Leu Pro Val Gln Glu
20 25 30

Asp Ala Gln Val Gly Thr Val Ile Ala Leu Ile Ser Val Ser Asp Arg
35 40 45

Asp Ser Gly Ala Asn Gly Gln Val Ile Cys Ser Leu Thr Pro His Val
50 55 60

Pro Phe Lys Leu Val Ser Thr Tyr Lys Asn Tyr Tyr Ser Leu Val Leu
65 70 75 80

Asp Ser Ala Leu Asp Arg Glu Ser Val Ser Ala Tyr Glu Leu Val Val
85 90 95

Thr Ala Arg Asp Gly Gly Ser Pro Ser Leu Trp Ala Thr Ala Arg Val
100 105 110

Ser Val Glu Val Ala Asp Val Asn Asp Asn Ala Pro Ala Phe Ala Gln
115 120 125

Pro Glu Tyr Thr Val Phe Val Lys Glu Asn Asn Pro Pro Gly Cys His
130 135 140

Ile Phe Thr Val Ser Ala Trp Asp Ala Asp Ala Gln Lys Asn Ala Leu
145 150 155 160

Val Ser Tyr Ser Leu Val Glu Arg Arg Val Gly Glu His Ala Leu Ser
165 170 175

Ser Tyr Val Ser Val His Ala Glu Ser Gly Lys Val Tyr Ala Leu Gln
180 185 190

Pro Leu Asp His Glu Glu Leu Glu Leu Leu Gln Phe Gln Val Ser Ala
195 200 205

Arg Asp Ala Gly Val Pro Pro Leu Gly Ser Asn Val Thr Leu Gln Val
210 215 220

Phe Val Leu Asp Glu Asn Asp Asn Ala Pro Ala Leu Leu Ala Thr Pro
225 230 235 240

Ala Gly Ser Ala Gly Gly Ala Val Ser Glu Leu Val Pro Arg Ser Val
245 250 255

Gly Ala Gly His Val Val Ala Lys Val Arg Ala Val Asp Ala Asp Ser
260 265 270

Gly Tyr Asn Ala Trp Leu Ser Tyr Glu Leu Gln Pro Ala Ala Val Gly
275 280 285

Ala His Ile Pro Phe His Val Gly Leu Tyr Thr Gly Glu Ile Ser Thr
290 295 300

Thr Arg Ile Leu Asp Glu Ala Asp Ala Pro Arg His Arg Leu Leu Val
305 310 315 320

Leu Val Lys Asp His Gly Glu Pro Ala Leu Thr Ser Thr Ala Thr Val
325 330 335

Leu Val Ser Leu Val Glu Asn Gly Gln Ala Pro Lys Thr Ser Ser Arg
340 345 350

Ala Ser Val Gly Ala Val Asp Pro Glu Ala Ala Leu Val Asp Ile Asn
 355 360 365

Val Tyr Leu Ile Ile Ala Ile Cys Ala Val Ser Ser Leu Leu Val Leu
 370 375 380

Thr Leu Leu Leu Tyr Thr Ala Leu Arg Cys Ser Ala Pro Pro Thr Val
 385 390 395 400

Ser Arg Cys Ala Pro Gly Lys Pro Thr Leu Val Cys Ser Ser Ala Val
 405 410 415

Gly Ser Trp Ser Tyr Ser Gln Gln Arg Arg Gln Arg Val Cys Ser Ala
 420 425 430

Glu Ser Pro Pro Lys Thr Asp Leu Met Ala Phe Ser Pro Ser Leu Gln
 435 440 445

Leu Ser Arg Glu Asp Cys Leu Asn Pro Pro Ser Glu Pro Arg Gln Pro
 450 455 460

Asn Pro Asp Trp Arg Tyr Ser Ala Ser Leu Arg Ala Gly Met His Ser
 465 470 475 480

Ser Val His Leu Glu Glu Ala Gly Ile Leu Arg Ala Gly Pro Gly Gly
 485 490 495

Pro Asp Gln Gln Trp Pro Thr Val Ser Ser Ala Thr Pro Glu Pro Glu
 500 505 510

Ala Gly Glu Val Ser Pro Pro Val Gly Ala Gly Val Asn Ser Asn Ser
 515 520 525

Trp Thr Phe Lys Tyr Gly Pro Gly Asn Pro Lys Gln Ser Gly Pro Gly
 530 535 540

Glu Leu Pro Asp Lys Phe Ile Ile Pro Gly Ser Pro Ala Ile Ile Ser

545	550	555	560
Ile Arg Gln Glu Pro Thr Asn Ser Gln Ile Asp Lys Ser Asp Phe Ile			
	565	570	575
Thr Phe Gly Lys Lys Glu Glu Thr Lys Lys Lys Lys Lys Lys Lys Lys			
	580	585	590
Gly Asn Lys Thr Gln Glu Lys Lys Glu Lys Gly Asn Ser Thr Thr Asp			
	595	600	605
Asn Ser Asp Gln			
610			

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 Synthesized Oligo-cap Linker

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